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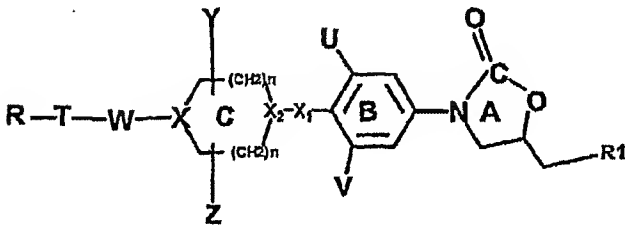
(54) Title: OXAZOLIDINONE DERIVATIVES AS ANTIMICROBIALS



(I)

(57) Abstract: The present invention relates to certain substituted phenyl oxazolidinones of the formula h wherein T is a ring and to the processes for the synthesis of the same. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms such as Bactericides spp. and Clostridia spp. species, and acid fast organisms such as Mycobacterium tuberculosis, Mycobacterium avium and Mycobacterium tuberculosis, Mycobacterium avium and Mycobacterium spp.

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OXAZOLIDINONE DERIVATIVES AS ANTIMICROBIALS

FIELD OF THE INVENTION

The present invention relates to certain substituted phenyl oxazolidinones and to the processes for the synthesis of the same. This invention also relates to pharmaceutical compositions containing the compounds of the present invention as antimicrobials. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms such as Bacterioides spp. and Clostridia spp. species, and acid fast organisms such as Mycobacterium tuberculosis, Mycobacterium avium and Mycobacterium spp.

BACKGROUND OF THE INVENTION

Increasing antibacterial resistance in Gram positive bacteria has presented a formidable treatment problem. The enterococci, although traditionally non virulent pathogens, have been shown, when associated with Vancomycin resistance, to have an attributable mortality of approximately 40%. Staphylococcus aureus, the traditional pathogen of post operative wounds, has been resistant to Penicillin due to production of penicillinases. This resistance was overcome by the development of various penicillinase stable β lactams. But the pathogen responded by synthesizing a modified target penicillin binding protein- 2' leading to less affinity for β lactam antibiotics and a phenotype known as Methicillin Resistant S. aureus (MRSA). These strains, till recently were susceptible to Vancomycin, which inspite of its various drawbacks, has become the drug of choice for MRSA infections. Streptococcus pneumoniae is a major pathogen causing pneumonia, sinusitis and meningitis. Until very recently it was highly susceptible to penicillin. Recently though, different PBP 2' strains with different susceptibility to penicillin have been reported from across the globe.

Oxazolidinones are a new class of synthetic antimicrobial agents which kill gram positive pathogens by inhibiting a very early stage of protein synthesis. Oxazolidinones inhibit the formation of ribosomal initiation complex involving 30S and 50S ribosomes leading to prevention of initiation complex formation. Due to their novel mechanism of

action, these compounds are active against pathogens resistant to other clinically useful antibiotics.

WO 02/06278 application discloses phenyloxazolidinone derivatives as antimicrobials.

WO 01/46164 discloses piperidinyloxy and pyrrolidinyloxyphenyl oxazolidinones as antimicrobials.

Bioorganic &Medicinal Chemistry Letters 11 (2001) 1829-1832 discloses piperidinyloxy oxazolidinone anitimicrobial agents

WO 99/37630 discloses oxazolidinone combinatorial libraries.

WO 93/23384 application discloses phenyloxazolidinones containing a substituted diazine moiety and their uses as antimicrobials.

WO 93/09103 application discloses substituted aryl and heteroaryl- phenyl-oxazolidinones useful as antibacterial agents

WO 90/02744 application discloses 5-indolinyl-5β-amidomethyloxazolidinones, 3-(fused ring substituted) phenyl-5β-amidomethyloxazolidinones which are useful as antibacterial agents.

European Patent Publication 352,781 discloses phenyl and pyridyl substituted phenyl oxazolidinones.

European Patent Application 312,000 discloses phenylmethyl and pyridinylmethyl substituted phenyl oxazolidinones.

U.S. Patent No. 5,254,577 discloses nitrogen heteroaromatic rings attached to phenyloxazolidinone.

U.S. Patents No. 5,547,950 and 5,700,799 also disclose the phenyl piperazinyl oxazolidinones.

Other references disclosing various phenyloxazolidinones include U.S. Patent Nos. 4,801,600 and 4,921,869; Gregory W.A., *et al.*, *J.Med.Chem.*, 1989; 32: 1673-81; Gregory W.A., *et al.*, *J.Med.Chem.*, 1990; 33: 2569-78; Wang C., *et al.*, *Tetrahedron*, 1989; 45: 1323-26; Brittelli, *et al.*, *J.Med. Chem.*, 1992; 35: 1156; and *Bio-organic and Medicinal Chemistry Letters*, 1999; 9: 2679-2684; Antibacterial & Antifungal Drug Discovery & Development Summit, Strategic Research Institute, June 28-29, 2001, Amsterdam, The

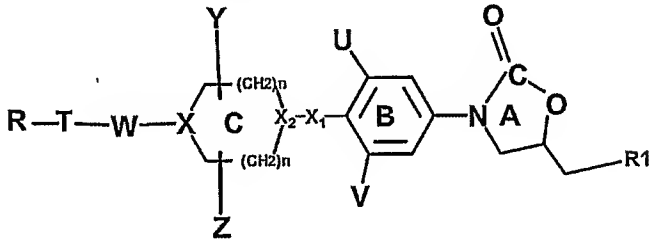
Netherlands; Posters No. 1822, 1823, 1824, 1825, 1826, 1827, 1828, 1829, 1830, 1831, 1832, 1833, and 1834, 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Sept 17-20, 2000, Toronto, Canada; and Posters No 1023, 1040, 1041, 1042, 1043, 1044,1045, 1046, 1047, 1048, 1049, 1050, and 1051, 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Sept 22-25, 2001, Chicago, USA.

SUMMARY OF THE INVENTION

The invention involves the synthesis, identification and profiling of oxazolidinone molecules which have good activity against multiply resistant gram positive pathogens like MRSA, VRE and PRSP. Some of these molecules have activity against MDR-TB and MAI strains, while others have significant activity against important anaerobic bacteria.

The invention provides processes for phenyloxazolidinones derivatives which can exhibit significant antibacterial activity against multiply resistant gram positive pathogens like MRSA, VRE and PRSP against MDR-TB and MAI strains, in order to provide safe and effective treatment of bacterial infections.

In accordance with one aspect of the present invention, there are provided compounds having the structure of Formula I



FORMULA I

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, or metabolites, wherein

T is a five to seven membered heterocyclic ring, aryl, substituted aryl, bound to the ring **C** with a linker W. Preferred forms of **T** are selected from aryl and five membered heteroaryl which are further substituted by a group represented by **R**, wherein R is selected from the group consisting of H, C_{1-6} alkyl, F, Cl, Br,I, –CN, COR_5,$COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, CON (R_6, R_7), CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH = N-OR_{10}, -C=CH-R_5, OR_5, SR_5, $-C(R_9)=C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl,

Br, I, OR_4, SR_4, wherein R_4 and R_5 are independently selected from H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl, heteroaryl; R_6 and R_7, are independently selected from H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently selected from H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl;

n is an integer in the range from 0 to 3;

X is H, CH, CH-S, CH-O, N, $CHNR_{11}$, wherein R_{11} is hydrogen, optionally substituted C_{1-2} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyl carboxy, aryl or heteroaryl;

X_1 is $(CH_2)_nS$, $(CH_2)_nO$, where n = 0 to 3; NR_{11} wherein R_{11} is the same as defined above; C=O, or C=S;

X_2 = CH or N;

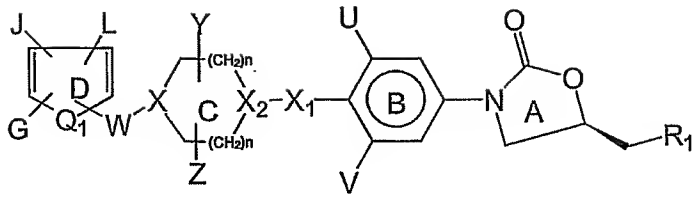
Y and Z are independently selected from hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl or C_{0-3} bridging group;

U and V are independently selected from hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, preferably U and V are hydrogen or fluoro;

W is selected from CH_2, CO, CH_2NH, $-NHCH_2$, $-CH_2NHCH_2$, $-CH_2N(R_{11})CH_2-$, $CH_2(R_{11})N-$, $CH(R_{11})$, $CH_2(CO)$, NH, O, S, $N(R_{11})$, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, $N(R_{11})CSN(R_{11})$, SO_2, SO, wherein R_{11} is the same as defined above; and

R_1 is selected from $-NHC(=O)R_2$, $N(R_3, R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$, wherein R_2 is hydrogen, aryl, heteroaryl, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; or thioC_{1-6} alkyl; R_3, R_4 are independently selected from hydrogen, aryl, heteroaryl, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH.

In accordance with a second aspect of the present invention, there are provided compounds represented by Formula II containing D ring as furanyl, thienyl, and pyrrolyl ring systems and further substituted by substitutions G, J and L,



Formula II

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, or metabolites, wherein

R_1 is selected from $-NHC(=O)R_2$, $-N(R_3, R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$ wherein R_2, R_3, R_4 are independently hydrogen, aryl, heteroaryl, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I, OH; preferably R_1 is of the formula $-NH(C=O)X_3$ wherein X_3 is CH_3, CH_2F, CHF_2, CF_3, CH_2Cl, $CHCl_2$ or CCl_3;

U and V are independently selected from hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I; preferably U and V are hydrogen and fluoro;

Y and Z are independently selected from hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{0-3} bridging group;

X is selected from H, CH, CH-S, CH-O or N;

X_1 is $(CH_2)_nS$, $(CH_2)_nO$, where n = 0 to 3; NR_{11}, wherein R_{11} is hydrogen, optionally substituted C_{1-2} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyl carboxy, aryl or heteroaryl; C=O, C=S;

X_2 = CH or N;

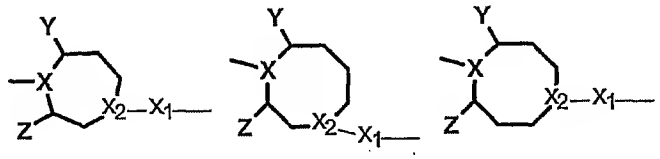
W is independently selected from CH_2, C=O, CH_2NH, $NHCH_2$, CH_2NHCH_2, $CH_2N(R_{11})CH_2$, $CH_2N(R_{11})$, $CH(R_{11})$, $CH_2(C=O)$, NH, O, S, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, SO_2, SO, $N(R_{11})$, $N(R_{11})C(=S)N(R_{11})$, wherein R_{11} is the same as defined above;

Q_1 is selected from O, S or NR_{11}, wherein R_{11} is as defined above;

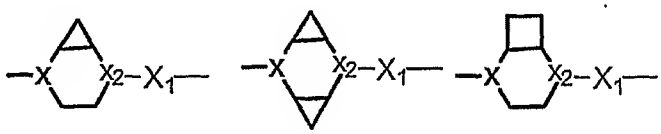
G, J, L are independently selected from H, C_{1-6} alkyl, F, Cl, Br,I, –CN, COR_5,$COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, CON (R_6, R_7), CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH = N-OR_{10}, -C=CH-R_5, OR_5, SR_5, $-C(R_9)=C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4, SR_4, wherein R_4, R_5 are independently selected from H, C_{1-12} alkyl, C_{3-12}

cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl, heteroaryl; R_6 and R_7 are independently selected from H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently selected from H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl, heteroaryl; except when W=CO, Q_1=O, S, X=N, X_2=CH, X_1=O and G, J, L=H.

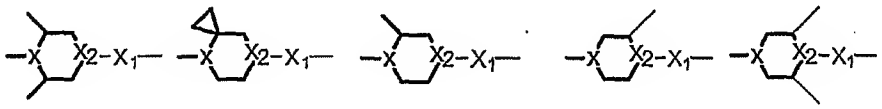
In some compounds represented by Formula II, ring C may be 6-8 membered in size and the ring may have either two or three carbon atoms between each nitrogen atom, for example:



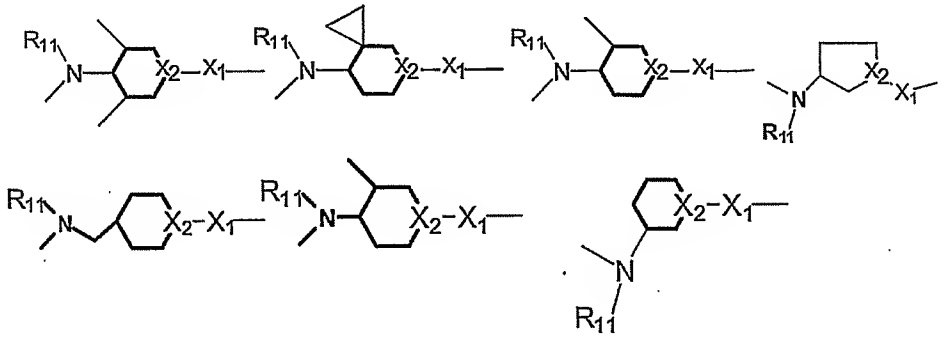
The ring C may be bridged to form a bicyclic system as shown below:



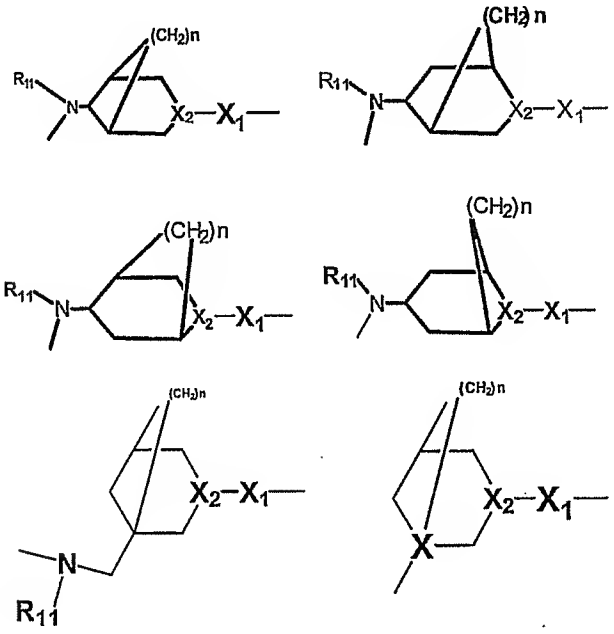
When ring C is optionally substituted at positions Y and Z with alkyl groups, cycloalkyl groups, fluoro group, carboxylic and corresponding esters, amides, substituted alkyls or bridging alkyl groups are as shown below:



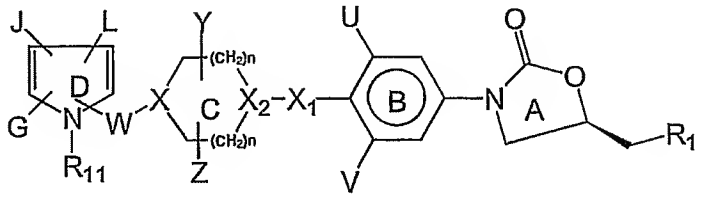
When ring C is 6 membered in size and X is -CH-(NHR), or >CCH_2NHR-, the following rings are preferred ones wherein R_{11} is the same as defined earlier.



In addition to the above, ring C also includes the following structures:



In accordance with a third aspect of the present invention, there are provided compounds represented by Formula III



FORMULA III

wherein

$\mathbf{R_1}$ is selected from –NHC(=O)R_2, -N(R_3, R_4), –NR_2C(=S)R_3, –NR_2C(=S)SR_3 wherein R_2, R_3, R_4 are independently hydrogen, aryl, heteroaryl, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I, OH; preferably $\mathbf{R_1}$ is of the formula –NH(C=O)X_3 or NH(C=S)X_3 wherein X_3 is CH_3, CH_2F, CHF_2, CF_3, CH_2Cl, $CHCl_2$ or CCl_3;

U and **V** are independently selected from hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I; preferably U and V are hydrogen and fluoro;

Y and **Z** are independently selected from hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{0-3} bridging group;

X is selected from H, CH, CH-S, CH-O or N;

$\mathbf{X_1}$ is $(CH_2)_nS$, $(CH_2)_nO$, where n = 0 to 3; NR_{11}, wherein R_{11} is hydrogen, optionally substituted C_{1-2} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyl carboxy, aryl or heteroaryl; C=O, C=S;

$\mathbf{X_2}$ = CH or N;

W is independently selected from CH_2, CO, CH_2NH, -$NHCH_2$, -CH_2NHCH_2, -CH_2-N(R_{11}) CH_2 -, CH_2 (R_{11})N -, CH(R_{11}), CH_2(CO), NH, O, S, N(R_{11}), (CO)CH_2, N(R_{11})CON(R_{11}), N(R_{11})C(=S)N(R_{11}), SO_2, SO, wherein R_{11} is the same as defined above;

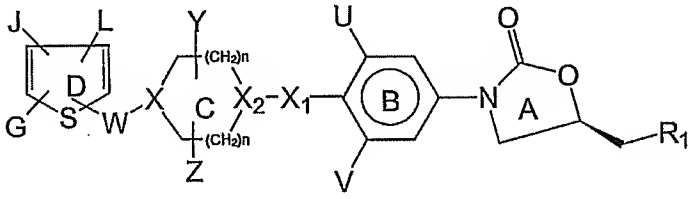
G, J, L are independently selected from H, C_{1-6} alkyl, F, Cl, Br,I, –CN, COR_5,$COOR_5$, N(R_6,R_7), NHCOC(R_8, R_9, R_{10}), CON (R_6, R_7), CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH = N-OR_{10}, -C=CH-R_5, OR_5, SR_5, -C(R_9)=C(R_9)NO_2, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4, SR_4, wherein R_4, R_5 are independently selected from H; C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl, heteroaryl; R_6 and R_7 are independently selected from H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently selected from H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, N(R_6,R_7); R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl, heteroaryl; and

n is an integer in the range from 0 to 3;

Particular G, J and L substitutions can include nitro, aldehydes and halides.

Preferably W is selected from the group consisting of CH_2, C(=O), C(=O)-C(=O), CH_2NH, $-NHCH_2$, $-CH_2NHCH_2$, $-CH_2-N(CH3)CH_2-$, CH_2 (CH_3)N -, CH (CH_3), S and CH_2(C=O), -NH.

In accordance with a fourth aspect of the present invention, there are provided compounds represented by Formula IV



FORMULA IV

wherein

R_1 is selected from $-NHC(=O)R_2$, $-N(R_3, R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$ wherein R_2, R_3, R_4 are independently hydrogen, aryl, heteroaryl, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I, OH; preferably R_1 is of the formula $-NH(C=O)X_3$ wherein X_3 is CH_3, CH_2F, CHF_2, CF_3, CH_2Cl, $CHCl_2$, CCl_3;

U and V are independently selected from hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I; preferably U and V are hydrogen and fluoro;

Y and Z are independently selected from hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{0-3} bridging group;

X is selected from C, CH, CH-S, CH-O or N;

X_1 is $(CH_2)_nS$, $(CH_2)_nO$, where n = 0 to 3; NR_{11}, wherein R_{11} is hydrogen, optionally substituted C_{1-2} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyl carboxy, aryl or heteroaryl; C=O, C=S;

X_2 = CH or N;

W is independently selected from CH_2, CO, CH_2NH, $-NHCH_2$, $-CH_2NHCH_2$, $-CH_2-N(R_{11})CH_2$ -, $CH_2(R_{11})N-$, $CH(R_{11})$, CH_2(CO), NH, O, S, $N(R_{11})$, $(CO)CH_2$,

$N(R_{11})CON(R_{11})$, $N(R_{11})C(=S)N(R_{11})$, SO_2, SO, wherein R_{11} is the same as defined above;

G, J, L are independently selected from H, C_{1-6} alkyl, F, Cl, Br,I, –CN, COR_5,$COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, $CON(R_6, R_7)$, CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH = N-OR_{10}, -C=CH-R_5, OR_5, SR_5, $-C(R_9)=C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4, SR_4; wherein R_4, R_5 are independently selected from H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl, heteroaryl; R_6 and R_7 are independently selected from H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently selected from H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, $N(R_6, R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl, heteroaryl; except when W=CO, X=N, X_2=CH, X_1=O, G, J, L=H; and

n is an integer in the range from 0 to 3;

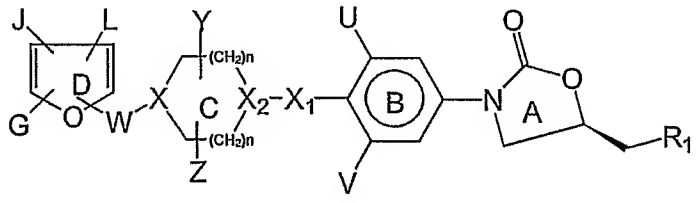
Particular G, J and L substitutions include nitro, aldehydes or halides;

Preferably W is selected from the group consisting of CH_2, C(=O), C(=O)-C(=O), CH_2NH, $-NHCH_2$, $-CH_2NHCH_2$, $-CH_2-N(CH_3)CH_2-$, CH_2 (CH_3)N -, CH (CH_3), S and CH_2(C=O), -NH.

Another particular compound of Formula IV is as follows:

(S)-N-[[3-[3-Fluoro-4-[N-{2-thienyl-(5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide.

In accordance with a fifth aspect of the present invention, there are provided compounds represented by Formula V



FORMULA V

wherein

R_1 is selected from –NHC(=O)R_2, -N(R_3, R_4), –NR_2C(=S)R_3, –NR_2C(=S)SR_3 wherein R_2, R_3, R_4 are independently hydrogen, aryl, heteroaryl, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I, OH; preferably R_1 is of the formula –NH(C=O)X_3 wherein X_3 is CH_3, CH_2F, CHF_2, CF_3, CH_2Cl, $CHCl_2$ or CCl_3;

U and V are independently selected from hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I; preferably U and V are hydrogen and fluoro;

Y and Z are independently selected from hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{0-3} bridging group;

X is selected from H, CH, CH-S, CH-O, or N;

X_1 is $(CH_2)_nS$, $(CH_2)_nO$, where n = 0 to 3; NR_{11}, wherein R_{11} is hydrogen, optionally substituted C_{1-2} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyl carboxy, aryl or heteroaryl; C=O, C=S;

X_2 = CH or N;

W is independently selected from CH_2, CO, CH_2NH, -$NHCH_2$, -CH_2NHCH_2, -CH_2-N(R_{11})CH_2 -, CH_2(R_{11})N -, CH (R_{11}), CH_2(CO), NH, O, S, N(R_{11}), (CO)CH_2, N(R_{11})CON(R_{11}), N(R_{11})C(=S)N(R_{11}), SO_2, SO, wherein R_{11} is the same as defined above;

G, J, L are independently selected from H, C_{1-6} alkyl, F, Cl, Br,I, –CN, COR_5,$COOR_5$, N(R_6,R_7), NHCOC(R_8, R_9, R_{10}), CON (R_6, R_7), CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH = N-OR_{10}, -C=CH-R_5, OR_5, SR_5, -C(R_9)=C(R_9)NO_2, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4, SR_4; wherein R_4, R_5 are independently selected from H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl, heteroaryl; R_6 and R_7, are independently selected from H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently selected from H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, N(R_6,R_7); R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl; except when W=CO, X=N, X_2=CH, X_1=O, G, J, L=H; and

n is an integer in the range from 0 to 3.

Particular G, J and L substitutions are nitro, aldehydes and halides.

Preferably W is selected from the group consisting of CH_2, C(=O), C(=O)-C(=O), CH_2NH, $-NHCH_2$, $-CH_2NHCH_2$, $-CH_2-N(CH_3)CH_2-$, CH_2 (CH_3)N -, CH (CH_3), S and CH_2(C=O), -NH.

A particular compound of Formula V is as follows:

(S)-N-[[3-[3-Fluoro-4-[N-{2-furyl-(5-nitro)-methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide.

Compounds of the present invention can be useful antimicrobial agents, effective against a number of human and veterinary pathogens, particularly aerobic Gram-positive bacteria, including multiply-antibiotic resistant staphylococci and streptococci, as well as anaerobic organisms such as Mycobacterium tuberculosis and other mycobacterium species.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, suppositories, and ointments. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, or tablets disintegrating agents; it can also be as finely divided solid which is in admixture with the finely divided active compound. For the preparation of tablets, the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 5 to about 70 percent of the active ingredient. Suitable solid carriers are lactose, pectin, dextrin, starch, gelatin, tragacanth, low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions, suspensions, and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. Such solutions are prepared so as to be acceptable to biological systems (isotonicity, pH, etc.). Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by

dissolving the active component in water and adding suitable colorants, flavours, stabilizing, and thickening agents as desired. Aqueous suspension suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other well-known suspending agents.

Ointment preparations contain heavy metal salts of a compound of Formula I with a physiologically acceptable carrier. The carrier is desirably a conventional water-dispersible hydrophilic or oil-in-water carrier, particularly a conventional semi-soft or cream-like water-dispersible or water soluble, oil-in-water emulsion infected surface with a minimum of discomfort. Suitable compositions may be prepared by merely incorporating or homogeneously admixing finely divided compounds with the hydrophilic carrier or base or ointment.

The pharmaceutical preparations can be in unit dosage form. In such forms, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete capsules, powders in vials or ampoules, and ointments capsule, cachet, tablet, gel, or cream itself or it can be the appropriate number of any of these packaged forms.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from less than 1 mg to several grams according to the particular application and the potency of the active ingredient.

In therapeutic use as agents for treating bacterial infections the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 3 mg to about 40 mg per kilogram daily. The dosages, however, may be varied depending upon the requirements of the patient and the compound being employed. Determination of the proper dosage for a particular situation is within the smaller dosages which are less than the optimum dose. Small increments until the optimum effect under the daily dosage may be divided and administered in portions during the day if desired.

In one aspect, the invention provides processes for the synthesis of compounds of Formulae I, II, III, IV and V. Pharmaceutically acceptable non-toxic acid addition salts of the compounds of the present invention of Formulae I, II, III, IV and V may be formed with inorganic or organic acids, by methods well known in the art.

The present invention also includes within its scope prodrugs of the compounds of Formulae I, II, III, IV and V. In general, such prodrugs will be functional derivatives of these compounds which readily get converted in vivo into defined compounds. Conventional procedures for the selection and preparation of suitable prodrugs are known to the artisan of ordinary skill in the art.

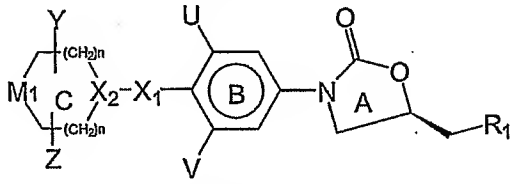
The invention also includes pharmaceutically acceptable salts, the enantiomers, diastereomers, N-oxides, prodrugs, metabolites in combination with a pharmaceutically acceptable carrier and optionally included excipients.

Other advantages of the invention will be set forth in the description which follows, and in part will be apparent from the description, or may be learned by the practice of the invention.

DETAILED DESCRIPTION OF THE INVENTION

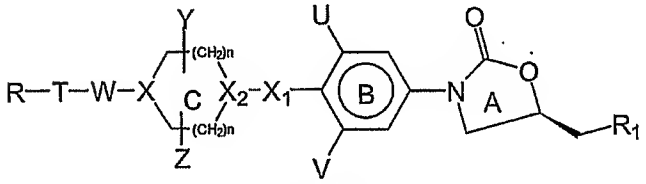
The compounds described herein represented by general Formula I may be prepared by the reaction sequence as shown in Scheme I:

SCHEME-I



FORMULA VI

R—T—W—R_{12}



FORMULA I

In Scheme I, the amine of structure of Formula VI wherein

M_1 is NH, NHR_{14}, CH_2NHR_{14}, $CH\text{-}CH_2NHR_{14}$, $\text{-}CCH_2\text{-}NHR_{14}$ wherein R_{14} is H, ethyl, methyl, isopropyl, acetyl, cyclopropyl, or alkoxy and

X_1 is $(CH_2)_nS$, $(CH_2)_nO$, where n = 0 to 3; NR_{11} wherein R_{11} is the same as defined above; C=O, C=S;

X_2 = CH or N;

Y and Z are independently selected from hydrogen, $C_{1\text{-}6}$ alkyl, $C_{3\text{-}12}$ cycloalkyl or $C_{0\text{-}3}$ bridging group;

U and V are independently selected from hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, preferably U and V are hydrogen or fluoro; and

R_1 is selected from -NHC(=O)R_2 , N(R_3, R_4), -NR_2C(=S)R_3, -NR_2C(=S)SR_3, wherein R_2 is hydrogen, aryl, heteroaryl, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; or thioC_{1-6} alkyl; R_3, R_4 are independently selected from hydrogen, aryl, heteroaryl, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH,

is reacted with a heteroaromatic compound of Formula R-T-W-R_{12} wherein

T is a five to seven membered heterocyclic ring, aryl, substituted aryl, bound to the ring **C** with a linker W. Preferred forms of **T** are selected from aryl and five membered heteroaryl which are further substituted by a group represented by **R**, wherein R is selected from the group comsisting of H, C_{1-6} alkyl, F, Cl, Br,I, –CN, COR_5,$COOR_5$, N(R_6,R_7), NHCOC(R_8, R_9, R_{10}), CON (R_6, R_7), CH_2NO_2, NO_2,. CH_2R_8, CHR_9, -CH = N-OR_{10}, -C=CH-R_5, OR_5, SR_5, -C(R_9)=C(R_9)NO_2, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4, SR_4; wherein R_4 and R_5 are independently selected from H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl, heteroaryl; R_6 and R_7, are independently selected from H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently selected from H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, N(R_6,R_7); R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl;

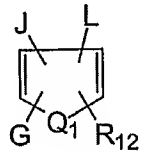
W is selected from CH_2, CO, CH_2NH, -$NHCH_2$, -CH_2NHCH_2, -$CH_2N(R_{11})CH_2$-, CH_2(R_{11})N-, CH(R_{11}), CH_2(CO), NH, O, S, N(R_{11}), (CO)CH_2, N(R_{11})CON(R_{11}), N(R_{11})CSN(R_{11}), SO_2, SO, wherein R_{11} is the same as defined above; and

R_{12} is a suitable leaving group well known to one of ordinary skill in the art such as fluoro, chloro, bromo, iodo, SCH_3, -SO_2CH_3, -SO_2CF_3, Tos or OC_6H_5 etc. The reaction can be carried out in a suitable solvent in the presence of a suitable base selected from the group consisting of potassium carbonate, N-ethyldiisopropylamine and dipotassium hydrogen phosphate.

For the preparation of compounds of Formula I when W is equal to CH_2, the corresponding aldehyde can be used through a process of reductive amination and is attached to the amine of Formula VI.

Similarly, for the preparation of compound of Formula I wherein W is equal to C = O, the corresponding acid can be used and the amino compound of Formula VI can be acylated through activated esters in the presence of condensing agents such as 1,3-dicyclohexylcarbodiimide (DCC) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC). Other methods of acylation can also be employed.

Alternatively, the compounds having carbonyl link can also be made by reacting heteroaromatic compound of the Formula VII (wherein G, J, L, Q_1 & R_{12} are the same as defined earlier),



Formula VII

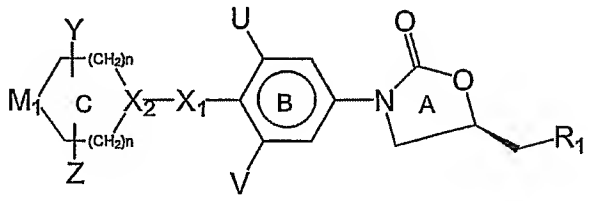
such as N-methyl pyrrole, with the intermediate amine of Formula VI in the presence of triphosgene or phosgene. The carbonyl linkers may also be introduced between hetero-aromatic compound, such as 3-bromothiophene and the amine of Formula VI with carbon monoxide in the presence of a catalyst such as Pd $(PPh_3)_2Cl_2$. The extended chain pyrroles having dicarbonyl linkers can also be obtained from treatment with oxalyl chloride and the amine of the Formula VI.

Alternatively, for the preparation of compounds of Formula I, the heteroaromatic compound of the Formula VII, such as 2-bromo-thiophene is reacted with the intermediate amine of Formula VI in the presence of ligands such as palladium dibenzylidene acetone $Pd_2(dba)_3$ or $Pd(OAc)_2$ with 2,2'-bis-(diphenylphosphino)-1,1'-binaphthyl (BINAP) and bases such as cesium carbonate or sodium t-butoxide (Ref: J. Org. Chem. **1999**, *64*, 6019-6022 and J. Org. Chem. **2000**, *65*, 1144-1157). Other ligands such as ethylenediamine or TMEDA along with bases such as cesium carbonate or potassium phosphate may also be used (Synlett, **2002**, *3*, 427-430)

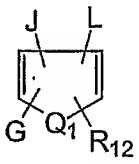
The reduction of the carbonyl linkers using the standard reducing agents results in the formation of methylene linkers.

The preparation of the compound of Formula II can be accomplished as exemplified below by three methods A, B and C as shown in Scheme II:

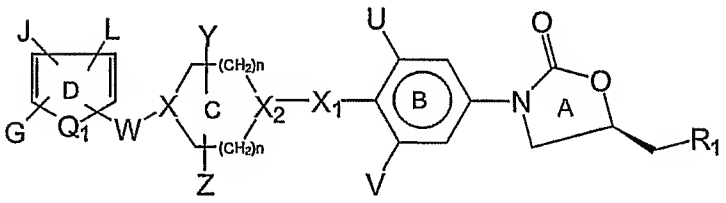
Scheme-II



Formula VI



Formula VII



Formula II

Method A:

The reductive alkylation of the amine intermediate of Formula VI with the corresponding heterocyclic aldehydes of the Formula VII, such as 5-nitro-2-furaldehyde (Q_1 = O; G=NO_2, J, L = H; R_{12} is CHO) using reducing agents well known to one of ordinary skill in the art such as sodium triacetoxyborohydride or sodium cyanoborohydride gives the products of Formula II wherein W=CH_2 as shown in Scheme II.

Alternatively, the compounds having carbonyl link can also be made by reacting heteroaromatic compound of the Formula VII, (wherein G, J, L, Q_1 and R_{12} are as defined earlier) such as N- methyl pyrrole with the intermediate amine of Formula VI in the

presence of triphosgene or phosgene. The carbonyl linkers may also be introduced between heteroaromatic compound, such as 3-bromothiophene and the amine of Formula VI with carbon monoxide in the presence of a catalyst such as Pd $(PPh_3)_2Cl_2$. The extended chain pyrroles having dicarbonyl linkers can also be obtained from treatment with oxalyl chloride and the amine of the Formula VI.

The reduction of the carbonyl linkers using the standard reducing agents results in the formation of methylene linkers.

Method B:

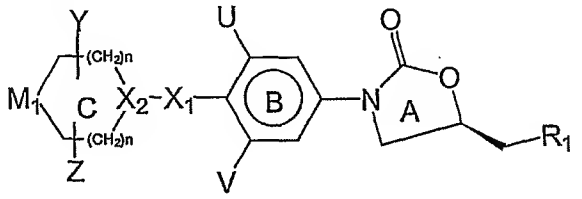
The amine of Formula VI is reacted with a heteroaromatic compound of Formula VII, such as 2-bromo-5-nitro thiophene where $Q_1 = S$, $G = NO_2$, J, $L = H$, $R_{12} = Br$, and R_{12} is a suitable leaving group which is the same as defined earlier for Scheme I.

The reaction can be carried out in a suitable solvent such as dimethylformamide, dimethylacetamide, ethanol, dimethylsulfoxide, acetonitrile, or ethylene glycol at a suitable temperature in the range of about -70°C to 180° C to afford compounds of Formula II. The presence of a suitable base such as triethylamine, N-ethyldiisopropyl amine, potassium carbonate, sodium bicarbonate, dipotassium hydrogen phosphate is useful in some cases to improve the yield of the reaction.

Method C:

The acylation of intermediate amines of Formula VI with a heterocyclic acid of Formula VII, such as 5-nitro-2- furoic acid (Q_1 = O; $G=NO_2$, J, L = H; R_{12} =COOH) gives products of Formula II, wherein W=CO as shown in the Scheme II wherein U, V, Y, Z, X, W, Q_1, G, J, L and R_{12} are the same as defined earlier.

Mainly three different amines of Formula VI



Formula VI

identified as three different cores, namely

(S)-N-[[3-{3-Fluoro-4-(piperidinyl-4-oxy)phenyl}-2-oxo-5-oxozolidinyl]methyl]acetamide (core I);

(S)-N-[[3-[3-Fluoro-4-[{(1α,5α,6α)-3-azabicyclo[3.1.0]hexan-6-yl}-methyloxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Core II);

(S)-N-[[3-[3-Fluoro-4-[N-1-(N-1-piperazinylcarbonyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (Core III);

were used for analoguing purposes wherein M, U, V, Y, Z, R_1, X_1, X_2 and n are as defined earlier.

The key intermediate amines of Formula VI for the analogue preparation were prepared from commercially available reagents. Some amines of Formula VI are already known in the literature and are given by reference and if they have been made for the first time or by different procedures or variation of known procedure they are described in detail in the experimental section.

The optically pure amines of Formula VI could be obtained either by one of a number of assymetric synthesis or alternatively by resolution from a racemic mixture by selective crystallization of a salt prepared, with an appropriate optically active acid such as dibenzoyl tartarate or 10-camphorsulfonic acid, followed by treatment with base to afford the optically pure amine.

The transformations effected are described in the experimental section. In the above synthetic methods where specific acids, bases, solvents, catalysts, oxidising agents, reducing agents etc. are mentioned, it is to be understood that the other acids, bases, solvents, catalysts, oxidising agents, reducing agents etc. may be used. Similarly, the reaction temperature and duration of the reaction may be adjusted according to the need.

An illustrative list of particular compounds according to the invention and capable of being produced by the above mentioned schemes include:

Compound No. Chemical Name

1. (S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl-(5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.1)
2. (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.2)
3. (S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl-(4-bromo-5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.3)

4. (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(4-bromo-5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.4)

5. (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(4-morpholino-5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.5)

6. (S)-N-[[3-[3-Fluoro-4-[N-1-[2-thienyl-{4-(N-4-methyl piperazin-1-yl)-5-nitro} methyl]piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.6)

7. (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(4-dimethylamino-5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.7)

8. (S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl-(4-isopropyl-5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.8)

9. (S)-N-[[3-[3-Fluoro-4-[N-1-[2-furyl-{5-(2-nitro)phenyl} methyl]piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.9)

10. (S)-N-[[3-[3-Fluoro-4-[N-1-[2-furyl-{5-(3-nitro)phenyl} methyl]piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.10)

11. (S)-N-[[3-[3-Fluoro-4-[N-1-{3-thienyl-(2-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.11)

12. (S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl-(5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]thioacetamide (Compound No.12)

13. (S)-N-[[3-[3-Fluoro-4-[N-1-{(benzo(b)furan-2-yl)methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.13)

14. (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(5-nitro)}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.14)

15. (S)-N-[[3-[3-Fluoro-4-[N-1-[1-{2-furyl-(5-nitro)}-ethyl] piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.15)

16. (S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl-(5-nitro)carbonyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.16)

17. (S)-N-[[3-[3-Fluoro-4-[N-1-{(benzo(b)furan-2-yl)carbonyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.17)

18. (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(5-nitro)carbonyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.18)

19. (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(5-nitro)thiocarbonyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]thioacetamide (Compound No.19)

20. (S)-N-[[3-[3-Fluoro-4-[{(1α,5α,6α)-3-t-butoxycarbonyl-3-azabicyclo[3.1.0]hexan-6-yl}-methyloxyl]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.20)

21. (S)-N-[[3-[3-Fluoro-4-[[(1α,5α,6α)-3-{2-furyl(5-nitro)methyl}-3-azabicyclo[3.1.0]hexan-6-yl]-methyloxyl]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.21)

22. (S)-N-[[3-[3-Fluoro-4-[[(1α,5α,6α)-3-{2-thienyl(5-nitro)methyl}-3-azabicyclo[3.1.0]hexan-6-yl]-methyloxyl]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.22)

23. (S)-N-[[3-[3-Fluoro-4-[{(1α,5α,6α)-3-(5-nitro-2-thienyl)-3-azabicyclo[3.1.0]hexan-6-yl}-methyloxyl]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.23)

24. (S)-N-[[3-[3-Fluoro-4-[N-1-(4-t-butoxycarbonyl)piperazinylcarbonyl] phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (Compound No.24)

25. (S)-N-[[3-[3-Fluoro-4-[N-1-[4-{2-furyl-(5-nitro)methyl}]piperazinylcarbonyl] phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (Compound No.25)

26. (S)-N-[[3-[3-Fluoro-4-[N-1-[4-{2-thienyl-(5-nitro)methyl}]piperazinylcarbonyl] phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (Compound No.26)

27. (S)-N-[[3-[3-Fluoro-4-[N-1-[4-{2-thienyl-(5-nitro)}]piperazinylcarbonyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (Compound No.27)

Most of the compounds were characterized using NMR, IR and were purified by chromatography. Crude products were subjected to column chromatographic purification using silica gel (100-200 or 60-120 mesh) as stationary phase.

The examples mentioned below demonstrate the general synthetic procedure as well as the specific preparation for the preparation for the preferred compound. The examples are given to illustrate the details of the invention and should not be constrained to limit the scope of the present invention.

EXAMPLE 1

Analogues of (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (core I)

(S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (core I) was prepared according to the procedure in Bioorganic & Medicinal Chemistry Letters 11 (2001) 1829-1832. The heteroaromatic group with the corresponding appendage can be introduced on the nitrogen atom of ring C of compounds of Formula I by one of the methods described below:

Method A

General Procedure:

The reductive alkylation of the amine intermediate of Formula VI with the corresponding heterocyclic aldehydes of the Formula VII, using known reducing agents well known to one of ordinary skill in the art such as sodium triacetoxyborohydride or sodium cyanoborohydride gave the products of Formula II wherein W=CH_2.

The following compounds were made using this method:

Compound No.1 (S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl-(5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide.

To a solution of compound (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (1.81 mmole) in THF, 5-nitro-furan-2-carboxaldehyde (2.36mmole) and molecular seive (4Å)were added at RT with stirring. After stirring for 15 min., sodium triacetoxy borohydride (5.45 mmole) was added and further stirred for 6-7hr at RT. The reaction mixture was filtered through celite bed and washed with THF. The filtrate was concentrated under reduced pressure. The residue obtained was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution (100ml) followed by brine wash (100ml). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product obtained was purified by column chromatography using 2-3% methanol in dichloromethane as eluent to yield 515 mg of the title compound.

H^1NMR ($CDCl_3$)δ PPM: 7.47-7.43 (d,1H), 7.05-6.97 (m,2H), 6.49-6.47 (d,1H), 6.10(m,1H), 4.78(m,1H), 4.38(m,1H), 4.01-3.98(t,1H), 3.77-3.62(m,5H), 2.79-2.76(m,2H), 2.45-2.42(m,2H), 2.02(s,3H), 1.97-1.94(m,2H).

Compound No.2 (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide and 5-nitro-2-thiophenecarboxaldehyde using Method A.

H^1NMR ($CDCl_3$)δ PPM: 7.8(S,1H), 7.49-7.45(d,1H), 7.08-6.96(m,3H), 6.09(m,1H), 4.76(m,1H), 4.36 (m,1H), 4.05-3.99(t,1H), 3.78-3.57(m,5H), 2.85(m,2H), 2.51(m,2H),2.03(s, 3H), 1.95(m,4H).

Compound No. 3 (S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl-(4-bromo-5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide and 4-bromo-5-nitro-2-furaldehyde using Method A.

H^1NMR ($CDCl_3$)δ PPM: 7.47-7.43(d,1H), 7.09-7.05(d,1H), 7.005-6.94(m,1H), 6.62(s,1H), 6.02-6.00(m,1H), 4.77-4.75(m,1H), 4.28(m,1H), 4.01(t,1H), 3.77-3.62(m,5H), 2.79-2.77(m,2H), 2.44(m,2H), 2.02(s,3H), 1.97-1.93(m,2H), 1.90-1.87(m,2H).

Compound No. 4 (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(4-bromo-5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide

The title compound was made with (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide and 4-bromo-5-nitro-2-thiophenecarboxaldehyde using Method A.

H^1NMR ($CDCl_3$)δ PPM: 7.48-7.44(d,1H), 7.08 7.06(d,1H), 7.01-6.98(d,1H), 6.92(s,1H), 6.00(m,1H), 4.77(m,1H), 4.33(m, 1H) .

Compound No. 5 (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(4-morpholino-5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide and 4-morpholino-5-nitro-2-thiophenecarboxaldehyde using Method A.

H^1NMR ($CDCl_3$)δ PPM: 7.47-7.43 (d, 1H), 7.05-6.98 (d, 1H), 6.57(s,1H), 6.00 (m,1H), 4.70 (m, 1H), 4.30 (m,1H), 4.01 (t, 1H), 3.89-3.86 (m,3H), 3.77-3.71 (m,2H), 3.64-3.60 (m,2H), 3.39-3.36 (m,5H), 2.75 (m,2H), 2.45 (m,2H), 2.02 (s,3H), 1.93 (m, 4H) .

Compound No. 6 (S)-N-[[3-[3-Fluoro-4-[N-1-[2-thienyl-{4-(N-4-methyl piperazin-1-yl)-5-nitro} methyl]piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide and 4-(N-4-methyl-piperazin-1-yl)-5-nitro-2-thiophenecarboxaldehyde using Method A.

H^1NMR ($CDCl_3$)δ PPM: 7.47-7.43 (d,1H), 7.07-6.95 (d,2H), 6.56 (s,1H), 6.02 (m,1H), 4.77-4.75 (m,1H), 4.31(m,1H), 4.04-3.98 (t,1H), 3.77-3.59 (m,5H), 3.41-3.40 (m,4H), 2.77 (m,2H), 2.60 (m,4H), 2.44 (m,2H), 2.36 (s,3H), 2.11 (s,3H), 2.02-1.89 (m,4H) .

Compound No. 7 (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(4-dimethylamino-5-nitro) methyl} piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide and 4-dimethylamino-5-nitro-2-thiophenecarboxaldehyde using Method A.

H^1NMR ($CDCl_3$)δ PPM: 7.48-7.44 (d,1H), 7.08-6.5 (m,2H), 6.54 (s,1H), 6.04 (m,1H), 4.77 (m,1H), 4.32 (m,1H), 4.05-3.99 (t,1H), 3.77-3.69 (m,5H), 3.11 (s,6H), 2.77 (m,2H), 2.45 (m,2H), 2.02 (s,3H), 1.96-1.91 (m,4H) .

Compound No. 8 (S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl-(4-isopropyl-5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide and 4-isopropyl-5-nitro-2-thiophenecarboxaldehyde using Method A.

H^1NMR ($CDCl_3$)δ PPM: 7.47-7.42 (d,1H), 7.07-6.95 (m,2H), 6.45 (s,1H), 6.11 (m,1H), 4.76 (m,1H), 4.28 (m,1`H), 4.05-3.99 (t,1H), 3.77-3.58 (m,5H), 2.8 (m,2H), 2.44 (m,2H), 2.17 (m,1H), 2.02 (s,3H), 1.98-1.87 (m,4H), 1.71 (s,6H) .

Compound No. 9 (S)-N-[[3-[3-Fluoro-4-[N-1-[2-furyl-{5-(2-nitro)phenyl} methyl]piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide and 5-(2-nitro)phenyl-2-furaldehyde using Method A.

H^1NMR ($CDCl_3$)δ PPM: 7.70-7.68 (d,2H), 7.67 (t,1H), 7.56-7.40 (m,2H), 7.04-6.98 (m,1H), 4.04-3.98 (t,1H), 3.75-3.59 (m,5H), 2.81-2.78 (m,2H), 2.39 (m,2H), 2.02 (s,3H), 1.87-1.85 (m,4H) .

Compound No. 10 (S)-N-[[3-[3-Fluoro-4-[N-1-[2-furyl-{5-(3-nitro)phenyl} methyl]piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide and 5-(3-nitro)phenyl-2-furaldehyde using Method A.

H^1NMR ($CDCl_3$)δ PPM: 8.47 (s,1H), 8.09-8.06 (d,1H), 7.96-7.94 (d,1H), 7.56-7.51 (t,1H), 7.46-7.411 (d,1H), 7.04-6.97 (m,2H), 6.76-6.75 (d,1H), 6.36-6.34 (d,1H), 5.98 (m,1H),

Compound No. 11(S)-N-[[3-[3-Fluoro-4-[N-1-{3-thienyl-(2-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide and 2-nitro-3-thiophenecarboxaldehyde using Method A.

H^1NMR ($CDCl_3$)δ PPM: 7.49-7.45 (m,1H), 7.20 (m,1H), 7.10-6.97 (m,2H), 6.04-6.03 (m,1H), 4.78-4.74 (m,1H), 4.32 (m,1H), 4.06-4.00 (m,2H), 3.78-3.56 (m,4H), 2.89 (m,2H), 2.42 (2H,m), 2.03 (s,3H), 1.94-1.82 (m,4H) .

Compound No. 12 (S)-N-[[3-[3-Fluoro-4-[N-{2-furyl-(5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]thioacetamide

To a solution of compound (S)-N-[[3-[3-Fluoro-4-[N-{2-furyl-(5-nitro)methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide

(0.48mmole) in toluene (20ml), Lawesson's reagent was added and it was heated to 70-80°C for 4-5 hr. The reaction mixture was cooled to RT and quenched with water and then extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue obtained was triturated with ether. The solid was filtered and dried to yield 30 mg of the title compound.

H^1NMR ($CDCl_3$)δ PPM: 7.94 (m,1H), 7.46-7.41 (d,1H), 7.29-7.28 (s,1H), 7.06-6.94 (m,2H), 6.51 (d,1H), 4.97-4.95 (m,1H), 4.30-4.23 (m,2H), 4.10-4.00 (m,2H), 3.83-3.80 (t,1H), 3.78-3.70 (m,2H), 2.81 (m,2H), 2.59 (s,3H), 2.47 (m,2H), 1.90 (m,4H).

Compound No. 13 (S)-N-[[3-[3-Fluoro-4-[N-{(benzo(b)furan-2-yl)methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide and benzo(b)furan-2-carboxaldehyde using Method A.

H^1NMR ($CDCl_3$)δ PPM: 7.54-7.46 (m,4H), 7.28-7.26 (s,1H), 7.05-6.99 (m,2H), 6.62 (s,1H), 6.30 (m,1H), 4.77-4.74 (m,1H), 4.28 (m,1H), 4.03-3.97 (t,1H), 3.71-3.60 (m,5H), 2.84 (m,2H), 2.48 (m,2H), 2.01 (s,3H), 1.92-1.91 (m,4H).

Method-B:

General procedure:

The amine of structure of Formula VI is reacted with a heteroaromatic compound of Formula VII having corresponding R_{12} appendages such as R_{13}, $-CH_2R_{13}$, $-COR_{13}$ or $-CH(CH_3)R_{13}$ wherein R_{13} is a suitable leaving group well known to one of ordinary skill in the art such as fluoro, chloro, bromo, SCH_3, $-SO_2CH_3$, $-SO_2CF_3$, Tos or OC_6H_5 etc.

The reaction is carried out in a suitable solvent such as dimethylformamide, dimethylacetamide, ethanol or ethylene glycol at a suitable temperature in the range of -78°C to 180°C to afford compounds of Formula II. The presence of a suitable base such as triethylamine, diisopropyl amine, potassium carbonate, sodium bicarbonate is useful in some cases to improve the yield of the reaction.

The following compounds were made following this method:

Compound No. 14 (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(5-nitro)}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide

To a solution of compound (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (0.665mmole) in DMSO (8ml), potassium carbonate (1.330mmole) and 2-bromo-5-nitro-thiophene (0.789mmole) were added and stirred for 14 hr at RT. The reaction mixture was quenched with water and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography using 1-2% methanol in dichloromethane as eluent to get the product, and triturated with ether. The solid obtained was filtered and dried to yield 130 mg of the title compound.

H^1NMR ($CDCl_3$)δ PPM: 7.80-7.78 (m,1H), 7.50 (dd,1H), 7.05 (t,1H), 6.03-5.97 (m,2H), 4.78-4.77 (m,1H), 4.55-4.52 (m,1H), 4.03 (t,1H), 3.77 (t,1H), 3.74-3.62 (m,4H), 3.44-3.36 (m,2H), 2.07-2.05 (m,4H), 2.03 (s,3H).

Compound No. 15 (S)-N-[[3-[3-Fluoro-4-[N-1-[1-{2-furyl-(5-nitro)-}-ethyl] piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide.

The tiltle compound was prepared from (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide and 5-nitro-2-(α-trifluoromethylsulfonate)ethylfuran using Method B.

H^1NMR ($CDCl_3$)δ PPM: 7.51-7.45 (1H,d), 7.26 (1H,s), 7.07-7.02 (1H,d), 6.99-6.97 (1H,d), 6.42-6.41(1H,s), 6.05 (1H,m), 4.77-4.76(1H,m), 4.32 (1H,m), 4.05-3.99 (1H,t), 3.79-3.68 (4H,m), 3.1(2H,m), 2.61 (2H,m), 2.03-2.01 (3H,s), 1.97-1.94(4H,m), 1.30(3H,d).

Method C:

General Procedure:

The compound of Formula I wherein W is equal to C=O is prepared from the corresponding acid of Formula VII and the amine of Formula VI is acylated through activated esters in the presence of condensing agents such as 1,3-dicyclohexylcarbodiimide (DCC) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), along with 1-hydroxybenzotriazole. Other methods of acylation can also be employed.

The following compounds were prepared using this method:

Compound No. 16 (S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl-(5-nitro)carbonyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide

To a solution of compound (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide in DMF, N-methyl morpholine (NMM) (1.064mmole), 1-hydroxybenzotriazole (HOBT) (1.064mmole), & 5-nitro-2-furoic acid (0.975mmole) were added at 0°C and stirred at the same temperature for 1hr. EDC (1.064mmole) was added at 0°C and the temperature was brought to room temperature over a period of 1hr and then stirred the reaction mixture for 14 hr at room temperature. The reaction mixture was quenched with water and extracted with ethyl acetate (100 ml). The organic layer was dried over anhydrous sodium sulfate and concentrated to get the crude product which was purified by column chromatography using 2-3% methanol in dichloromethane as eluent to yield 150 mg of the title compound.

H^1NMR ($CDCl_3$)δ PPM: 7.92 (dd,1H), 7.68(d,1H), 7.24(m,1H,-NH), 7.16 (d,1H), 7.15-7.00 (m, 2H), 4.78 (m,1H), 4.57(m,1H), 4.02 (t,2H), 3.88-3.82 (m,4H), 3.64-3.62 (m,2H), 3.10 (m,4H), 2.01(s,3H).

M+1= 513

Compound No. 17 (S)-N-[[3-[3-Fluoro-4-[N-1-{(benzo(b)furan-2-yl)carbonyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide and benzo(b)-furan-2-carboxylic acid using Method C.

H^1NMR ($CDCl_3$)δ PPM: 7.66-7.63 (d,1H), 7.53-7.37 (m,3H), 7.31-7.29 (m,2H), 7.08-7.02 (m,2H), 6.16 (m,1H), 4.76 (m,1H), 4.55 (m,1H), 4.06-4.00 (m,2H), 3.89-3.84 (m,2H), .41 (m,4H),2.03 (s,3H), 2.00-1.96 (m,4H).

Compound No. 18 (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(5-nitro)carbonyl}piperidinyl-4-oxy] phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide and 5-nitro-2-thiophenecarboxylic acid using Method C.

H^1NMR ($CDCl_3$ +DMSO)δ PPM: 7.87 (d,1H), 7.69(m,1H), 7.52(dd,1H), 7.22 (d,1H), 7.11-7.00 (m,2H), 4.77 (m,1H),4.56 (m,1H), 4.02 (t,1H), 3.83-3.78 (m,5H), 3.67 (m,2H), 3.21 (m,4H), 1.99 (s,3H).

M+1 = 513

Compound No. 19 (S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(5-nitro)thiocarbonyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]thioacetamide

The title compound was prepared with (S)-N-[[3-[3-fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide and 5-nitro-2-thiophenecarboxylic acid using Method C.

H^1NMR ($CDCl_3$)δ PPM: 7.96 (m,1H),7.76 (d,1H), 7.48(dd,1H), 7.12-6.97 (m,3H), 5.00-4.98 (m,1H),4.63 (m,1H), 4.30-4.25(m,1H), 4.12-4.06(m,4H), 3.84 (t,1H), 3.71 (m,1H), 3.52-3.45 (m,1H), 2.60 (s,3H), 2.05 (m,4H).

EXAMPLE 2

Analogues of (S)-N-[[3-[3-Fluoro-4-[{(1α,5α,6α)-3-azabicyclo[3.1.0]hexan-6-yl}-methyloxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Core II)

(S)-N-[[3-[3-Fluoro-4-[{(1α,5α,6α)-3-azabicyclo[3.1.0]hexan-6-yl}-methyloxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Core II) was prepared according to the following procedure:

Step-a: Preparation of (1α,5α,6α)-6-hydroxymethyl-3-azabicyclo[3.1.0]-hexane:

To a solution of (1α,5α,6α)-3-benzyl-6-hydroxymethyl-3-azabicyclo[3.1.0]-hexane (20gm, 0.098 mole) in methanol (300), was added ammonium formate (15.5 gm, 0.246 mole) and Pd/C (8 gm, wet 5%) and the rection mixture was heated to 50°C for 8 hrs. It was then filtered through celite bed (hyflo), and washed with methanol (100ml). The filtrate was evaporated in vacuo to yield 11gm of the title compound.

^{1}H NMR (DMSO-d_6) δ PPM: 3.27 (d,2H), 2.82 (d,2H), 2.64 (d,2H), 1.20 (m,2H), 0.85 (m,1H) .

Step-b: Preparation of (1α,5α,6α)-3-tert-butoxycarbonyl-6-hydroxymethyl-3-azabicyclo[3.1.0]-hexane:

To a solution of [1α,5α,6α]6-hydroxymethyl-3-azabicyclo[3.1.0]hexane (11gm, 0.097 mole) in dichloromethane (200ml), triethylamine (17.5mL, 0.126 mole) was added and cooled to 0°C. It was followed by the dropwise addition of di tert- butoxydicarbonate (25.4gm, 0.116 mole) at 0 to 5°C and then stirred at room temperature for 4 hrs. The reaction mixture was diluted with dichloromethane (100ml), washed with saturated sodium bicarbonate solution (2 × 200ml), followed by brine wash (2× 100ml). The organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo to yield the crude product which was purified by column chromatography, using 10% ethylacatate in hexane as eluent to yield 8.0 gm of the desired compound.

^{1}H NMR ($CDCl_3$) δ PPM : 3.63-3.60 (d,2H), 3.53-3.47 (m,2H), 3.43-3.33 (m,2H), 1.75-1.64 (m,2H), 1.43 (s,9H) 0.97-0.90 (m,1H).

Step-c: Preparation of 3- fluoro- 4-[{(1α,5α,6α)-3-tert-butoxycarbonyl-3-azabicyclo-[3.1.0]hexan-6-yl}-methyloxy]nitrobenzene:

To a solution of potassium tert-butoxide (t- KOBu) (5.13 gm, 0.045 mole) in THF (100ml), (1α,5α,6α)-3-tert-butoxycarbonyl-6-hydroxymethyl-3-azabicyclo[3.1.0]hexane obained in step-b dissolved in (50ml) THF was added and cooled to 0 to 5°C. Then, 3,4, diflouro nitrobenzene (5.6 gm, 0.0352 mole) was added dropwise and stirred for 2h at room temperature. The reaction mixture was quenched with saturated NH_4Cl solution (50ml). The organic layer was separated. The aqueous layer was again extracted with ethyl acetate (200ml), the combined organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo. The crude product was purified by column chromatography (15% ethyl acetate : hexane) to yield 6.5 gm of the title compound.

^{1}H NMR ($CDCl_3$) δ PPM : 8.06-7.97 (m,2H), 7.02-6.96 (t,1H), 4.14-4.12 (m,1H), 4.00-3.94 (m,1H), 3.71-3.61 (m,2H), 3.41-3.38 (m,2H), 1.64 (m,2H), 1.34 (s,9H), 1.23-1.18 (m,1H).

Step-d: Preparation of 3-Fluoro-4-[{(1α,5α,6α)-3-tetrabutoxycarbonyl-3-azabicyclo[3.1.0]hexan-6-yl}methyloxy]aniline:

To a solution of 3-fluoro-4-[{(1α,5α,6α)-3-tert-butoxycarbonyl-3-azabicyclo-[3.1.0]hexan-6-yl}-methyloxy]nitrobenzene obtained in step-c (6gm) in methanol (100),

5% wet Pd/C (8gm) was added and shaken in a parr hydrogenation apparatus under 50 psi of hydrogen gas for 3h . Then the rection mixture was filtered over celite bed and washed with 50 ml of methanol. The filtrate was evaporated in vacuo to yield 5.5 gm of the title compound.

^{1}H NMR ($CDCl_3$) δ PPM: 6.80-6.77 (t, 1H, Ar), 6.45-6.41 (d, Ar), 6.34-6.32 (d, 1H-ArH), 3.89-3.86 (m, 1H), 3.76-3.74 (m, 1H), 3.70-3.56 (m, 2H), 3.53-3.51 (d, 2H), 3.34-3.32 (m, 2H, NH_2), 1.48 (m, 2H), 1.41 (s, 9H), 1.09-1.05 (m, 1H).

Step-e: Preparation of 3-Fluoro-4-[{(1α,5α,6α)-3-tetrabutoxycarbonyl-3-azabicyclo[3.1.0]-hexan-6-yl}methyloxy] benzyloxy carbonyl aniline:

To a solution of 3-Fluoro-4-[{(1α,5α,6α)-3-tetrabutoxycarbonyl-3-azabicyclo[3.1.0]hexan-6-yl}methyloxy]aniline obtained in step-d (D, 5.0 gm, 0.015 mole) in THF (150ml) cooled to 5°C, sodium bicarbonate (3.92 gm, 0.046 mole), was added and then benzylchloroformate (3.94 gm, 0.02 mole) was added dropwise at the same temperature . The reaction mixture was stirred at room temperature for 4 hrs and then filtered, washed with THF (50 ml). The filtrate was evaporated in *vacuo*. The residue obtained was triturated with hexane. The solid was filtered and dried to get the 5.0 gm of the title compound.

^{1}H NMR ($CDCl_3$) δ PPM: 7.38-7.33 (5H, Ar), 7.28 (d, 1H, Ar), 6.77-6.84 (m, 2H), 6.60 (m, 1H, -NH), 5.19 (d, 2H, $-COH_2$-Ar), 3.98-3.96 (m, 1H), 3.83-3.81 (m, 1H), 3.66-3.56 (m, 2H), 3.37-3.36 (m, 2H), 1.57 (m, 2H), 1.43 (s, 9H), 1.11-1.08 (m, 1H).

Step-f: Preparation of R(-)-3-[3-fluoro-4-[{(1α,5α,6α)-3-tetrabutoxycarbonyl-3-azabicyclo[3.1.0]hexan-6-yl}methyloxy]phenyl]5-hydroxymethyl-2-oxazolidinone :

To a solution of 3-Fluoro-4-[{(1α,5α,6α)-3-tetrabutoxycarbonyl-3-azabicyclo[3.1.0]-hexan-6-yl}methyloxy]benzyloxycarbonylaniline obtained in step-e (4.5 gm, 0.0098 mole) in dry THF (50ml) cooled to –78°C, butyl lithium (8.39 ml 15% soln in hexane, 0.0199 mole) was added under the presence of nitrogen. The reaction mixture was stirred at –78°C for 1.5hr, then R-glycidyl butyrate (1.70 gm, 0.0118 mole) was added and the reaction mixture was stirred at –78°C for 1hr and then at RT for 18 hr. The reaction mixture was quenched with saturated ammonium chloride solution (25 ml) and the organic layer was separated. The aqueous layer was again extracted with 200ml of ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo.

The crude product was purified by column chromatography (eluent is 2% methanol in dichloromethane) to yield 3.5 gm of the title compound.

^{1}H NMR ($CDCl_3$) δ PPM: 7.46 (d, 1H, Ar), 7.12 (d, 1H), 6.93 (t, 1H Ar), 4.76-4.71 (, 1H), 4.03-3.73 (m, 6H), 3.66-3.57 (m, 2H), 3.36-3.35 (m, 2H), 2.41 (m, 1H, -OH), 1.56 (m, 2H), 1.43 (s, 9H), 1.14-1.10 (m, 1H).

Step-g: Preparation of R(-)-3-[3-fluoro-4-[{(1α,5α,6α)-3-tetrabutoxycarbonyl-3-azabicyclo[3.1.0] hexan-6-yl}methyloxy]phenyl]5-methanesulphonyloxy-methyl-2-oxazolidinone:

To a solution of R(-)-3-[3-fluoro-4-[{(1α,5α,6α)-3-tetrabutoxycarbonyl-3-azabicyclo[3.1.0]hexan-6-yl}methyloxy]phenyl]5-hydroxymethyl-2-oxazolidinone (3.0gm, 0.0071 mole) in dichloromethane (25 ml) cooled to 0-5°C, triethylamine (1.077 gm, 0.0106 mole) and methanesulfonyl chloride (1.058 gm, 0.0092 mole) were added, and the reaction mixture was stirred for 4 hr. The reaction mixture was diluted with dichloromethane (25 ml) and washed with saturated sodium bicarbonate solution and brine. The organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo to yield 3.5 gm of the title compound.

Step-h: Preparation of S(-)-3-[3-fluoro-4-[{(1α,5α,6α)-3-tert-butoxycarbonyl-3-azabicyclo[3.1.0]hexa-6-yl}methyloxy]phenyl]5-azidomethyl-2-oxazolidinone:

To a solution of R(-)-3-[3-fluoro-4-[{(1α,5α,6α)-3-tetrabutoxycarbonyl-3-azabicyclo[3.1.0]hexan-6-yl}methyloxy]phenyl]5-methanesulphonyloxy-methyl-2-oxazolidinone (3.0 gm, 0.006 mole) in DMF (20 ml), sodium azide (1.20 gm, 0.018 mole) was added and the reaction mixture heated to 80°C for 4-5 hrs . The reaction mixture was filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in ethyl acetate (50 ml) and washed with water (2 ×50 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo to yield 2.2 gm of the title compound.

^{1}H NMR ($CDCl_3$) δ PPM: 7.45 (dd, 1H, Ar), 7.11 (d, 1H, Ar), 6.95 (t, 1H, Ar), 4.79-4.75 (m, 1H), 4.07-3.98 (q, 2H), 3.87-3.81 (q, 2H), 3.72-3.5 (m, 4H), 3.38-3.35 (m, 2H), 1.56 (m, 2H), 1.43 (s, 9H), 1.160-1.10 (m, 1H).

Step-i: Preparation of S(-)-3-[3-fluoro-4-[{(1α,5α,6α)-3-tert-butoxycarbonyl-3-azabicyclo[3.1.0]hexan-6-yl]phenyl]-5-aminomethyl-2-oxazolidinone:

To a solution of S(-)-3-[3-fluoro-4-[{(1α,5α,6α)-3-tert-butoxycarbonyl-3-azabicyclo[3.1.0]hexa-6-yl}methyloxy]phenyl]5-azidomethyl-2-oxazolidinone (2.0 gm, 0.0045 mole) in THF, triphenylphosphine was added and stirred for 2hr at RT. Water (1.28 ml) was added to the reaction mixture and heated to 40°C and stirred for 4hr. The reaction mixture was further stirred at RT for 14 hr. The reaction mixture was concentrated under reduced pressure. To the residue, water (100 ml) was added and acidified with 1N HCl (aq. solution) up to pH 2. It was washed with ether (3 ×50 ml). The aqueous layer was basified with 1N NaOH solution up to pH 12 and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated to get the 1.5 gm of the title compound.

H^1 NMR ($CDCl_3$) δ PPM: 7.65 (dd, 1H, Ar), 7.13 (d, 1H, ar), 6.94 (t, 1H, Ar), 4.67-4.65 (m, 1H), 4.01 (t, 2H), 3.85-3.79 (m, 2H), 3.65-3.57 (m, 2H), 3.38-3.35 (m, 2H), 3.13-3.09 (m, 1H), 3.01-2.96 (m, 1H), 1.52 (m, 2H), 1.43 (s, 9H), 1.15-1.10 (m, 1H)

Step-j: Preparation of (S)-N-[[3-[3-Fluoro-4-[{(1α,5α,6α)-3-t-butoxycarbonyl-3-azabicyclo[3.1.0]hexan-6-yl}-methyloxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide.

To a solution of S(-)-3-[3-fluoro-4-[{(1α,5α,6α)-3-tert-butoxycarbonyl-3-azabicyclo[3.1.0]hexan-6-yl]phenyl]-5-aminomethyl-2-oxazolidinone (I, 1.4 gm, 0.003 mole) in dichloromethane (50ml) cooled to 0-5°C, triethylamine (0.7 ml, 0.005 mole) and acetic anhydride (0.45 ml, 0.0043 mole) were added and stirred at RT for 4-6 hrs. The reaction mixture was diluted with dichloromethane (25 ml) and washed with saturated sodium bicarbonate, followed by brine. The combined organic layer was dried over anhydrous sodium sulfate and evaporated under vacuo to get the 1.3 gm of the title compound.

H^1 NMR ($CDCl_3$) δ PPM: 7.46 (dd, 1H, Ar), 7.06 (d, 1H, ar), 6.93 (t, 1H, Ar), 6.18-6.14 (m, 1H-NH), 4.78-4.75 (m, 1H), 4.04-3.98 (m, 2H), 3.77-3.75 (t, 1H), 3.75-3.57 (m, 5H0, 3.38-3.35 (m, 2H), 2.02 (s, 3H), 1.56 (m, 2H), 1.43 (s, 9H), 1.15-1.10 (m, 1H).

Step-k: Preparation of (S)-N-[[3-[3-Fluoro-4-[{(1α,5α,6α)-3-azabicyclo[3.1.0]hexan-6-yl}-methyloxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide.

To a solution of compound (S)-N-[[3-[3-Fluoro-4-[{(1α,5α,6α)-3-t-butoxycarbonyl-3-azabicyclo[3.1.0] hexan-6-yl}-methyloxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide in dichloromethane, trifluoroacetic acid (20% of the solvent used) was added at 0°C and

stirred at 0-25°C for 2-4 hr. The reaction mixture was concentrated under reduced pressure to get (S)-N-[[3-[3-Fluoro-4-[{(1α,5α,6α)-3-azabicyclo[3.1.0]hexan-6-yl}-methyloxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide.

Compound No. 20: (S)-N-[[3-[3-Fluoro-4-[{(1α,5α,6α)-3-t-butoxycarbonyl-3-azabicyclo[3.1.0]hexan-6-yl}-methyloxyl]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide.

The title compound was prepared as described in step-j, Example 2.

H^1NMR ($CDCl_3$)δ PPM: 7.48 (d,1H, Ar), 7.04(d,1H, Ar), 6.93(t,1H, Ar), 6.18-6.14(m,1H, -NH), 4.78-4.75(m,1H), 4.04-3.98(m,2H), 3.75(t,1H), 3.72-3.57(m,5H), 3.38-3.35(m,2H), 2.02(s,3H), 1.56 (m,2H), 1.43(s,9H), 1.14(m,1H).

Compound No. 21: (S)-N-[[3-[3-Fluoro-4-[[(1α,5α,6α)-3-{2-furyl(5-nitro)methyl}-3-azabicyclo[3.1.0]hexan-6-yl]-methyloxyl]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide.

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-[{(1α,5α,6α)-3-azabicyclo[3.1.0]hexan-6-yl}-methyloxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide and 5-nitro-2-furaldehyde using Method A.

H^1NMR ($CDCl_3$)δ PPM: 7.77(d,1H, Ar), 7.48(d,1H, Ar), 7.03(d,1H, Ar), 6.92(t,1H, Ar), 6.45(d,1H, Ar), 6.14(m,1H, -NH), 4.76(m,1H), 4.01(t,1H), 3.89-3.76(m,2H), 3.71-3.60(m,5H), 3.19-3.16(m,2H), 2.65-2.62(m,2H),2.02(s,3H), 1.70(m,1H), 1.53(m,2H).

Compound No. 22 (S)-N-[[3-[3-Fluoro-4-[[(1α,5α,6α)-3-{2-thienyl(5-nitro)methyl}-3-azabicyclo[3.1.0]hexan-6-yl]-methoxyl]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide.

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-[{(1α,5α,6α)-3-azabicyclo[3.1.0]hexan-6-yl}-methyloxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide and 5-nitro-2-thiophenecarboxaldehyde using Method A.

H^1NMR ($CDCl_3$)δ PPM: 7.77(d,1H Ar), 7.48(d,1H Ar), 7.07(d,1H, Ar), 6.96(t,1H, Ar), 6.81(d,1H, Ar), 6.05 m,1H, -NH), 4.77 (m,1H), 4.02(t,1H), 3.90-3.77(m,2H), 3.75-3.61(m,5H), 3.15(m,2H), 2.48(m,2H), 2.02(s,3H), 1.72 (m,1H), 1.48(m,2H).

Compound No. 23 (S)-N-[[3-[3-Fluoro-4-[{(1α,5α,6α)-3-(5-nitro-2-thienyl)-3-azabicyclo[3.1.0]hexan-6-yl}-methyloxyl]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide.

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-[{(1α,5α,6α)-3-azabicyclo[3.1.0]hexan-6-yl}-methyloxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide and 5-nitro-2-bromothiophene using Method B.

H^1NMR ($CDCl_3$)δ PPM: 7.77(d,1H, Ar), 7.48(d,1H, Ar), 7.07(d,1H,Ar), 6.94(t,1H,Ar), 6.00(m,1H,-NH), 5.74(d,1H, Ar), 4.76(m,1H), 4.04-3.97(m,3H), 3.78-3.72(m,2H), 3.65-3.49(m,5H), 2.02(s,3H), 1.89(m,2H), 1.23(m,1H).

EXAMPLE 3

Analogues of (S)-N-[[3-[3-Fluoro-4-[N-1-(N-1-piperazinylcarbonyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (Core III)

(S)-N-[[3-[3-Fluoro-4-[N-1-(N-1-piperazinylcarbonyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide trifluorocaetate

To (S)-N-[[3-[3-Fluoro-4-[N-1-(4-t-butoxycarbonyl)piperazinylcarbonyl] phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (0.4g, 0.86 mmol) in dichloromethane (8 ml) was added trifluoroacetic acid (2 ml). The reaction mixture was stirred for 2 hrs and evaporated in vacuo to give the title compound. This product was used as such in the subsequent steps without further characterization.

Compound No. 24 (S)-N-[[3-[3-Fluoro-4-[N-1-(4-t-butoxycarbonyl)piperazinylcarbonyl] phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

To (S)-N-[[3-[3-Fluoro-4-[N-1-(4-carboxy)piperazinylcarbonyl] phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (1.87 g, 5.7 mmol; prepared following the procedures disclosed in WO 99/37630) in N,N-dimethylformamide (50ml), N-1-t-butoxycarbonylpiperazine (1.06g, 5.7 mmol) was added and cooled to 5 °C. To this suspension, N-methylmorpholine (0.63 g, 6.3 mmol) and 1-hydroxybenzotriazole (0.77g, 5.7 mmol) were added. It was stirred for 15 min, then EDC was added and further stirred at RT for 17hrs. The reaction mixture was diluted with water and extracted with ethyl

acetate. The organic layer was washed with satd.sodium bicarbonate solution, water and brine, dried over anhyd.sodium sulphate and evaporated in vacuo. The product was triturated with diethylether and filtered to give 1.6 g of the final product.

H^1NMR ($CDCl_3$)δ PPM: 7.52 (dd, 1H), 7.42 (t, 1H), 7.22 (m,1H), 6.04 (t, 1H), 4.81 (m,1H), 4.06 (t, 1H), 3.81-3.2 (m,11H), 2.02 (s,3H), 1.47 (s,9H)

M+1 = 465, M-tBu = 409

Compound No. 25 (S)-N-[[3-[3-Fluoro-4-[N-1-[4-{2-furyl-(5-nitro)methyl}]piperazinylcarbonyl] phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-[N-1-(N-1-piperazinylcarbonyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide Trifluorocaetate and 5-nitro-2-furaldehyde using Method A.

m.p. 141-146°C, ^{1}HNMR (DMSO) δppm 8.25 (t, 1H), 7.67 (d, 1H), 7.55 (dd, 1H), 7.40 (m, 2H), 6.81 (d, 1H), 4.75 (m, 1H), 4.14 (t, 1H), 3.76 (m, 6H), 2.73 (m, 2H), 1.83 (s, 3H)

M+1 = 490

Compound No. 26 (S)-N-[[3-[3-Fluoro-4-[N-1-[4-{2-thienyl-(5-nitro)methyl}]piperazinylcarbonyl] phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-[N-1-(N-1-piperazinylcarbonyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide Trifluorocaetate and 5-nitro-2-thiophenecarboxaldehyde using Method A.

^{1}HNMR ($CDCl_3$) δppm 7.79 (d, 1H), 7.53 (dd, 1H), 7.24 (m, 1H), 6.88 (d, 1H), 5.94 (t, 1H), 4.81 (m,1H), 4.06 (t, 1H), 3.9-3.6 (m, 8H), 3.38 (m, 2H), 2.63 (m, 2H), 2.51 (m, 2H), 2.02 (s, 3H)

M+1 = 506

Compound No. 27 (S)-N-[[3-[3-Fluoro-4-[N-1-[4-{2-thienyl-(5-nitro)}]piperazinylcarbonyl] phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

The title compound was prepared from (S)-N-[[3-[3-Fluoro-4-[N-1-(N-1-piperazinylcarbonyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide trifluoroacetate and 5-nitro-2-bromothiophene using Method B.

^{1}HNMR ($CDCl_3$) δppm 8.25 (t, 1H), 7.94 (d, 1H), 7.62-7.35 (m, 3H), 6.36 (d, 1H), 4.77 (m, 1H), 4.18 (t, 1H), 3.8 (m, 4H), 1.84 (s, 3H)

M+1 = 492

Pharmacological Testing

The compounds of the invention display antibacterial activity when tested by the agar incorporation method. The following minimum inhibitory concentrations (μg/ml) were obtained for representative compounds of the invention which are given below in Table-1.

GUIDE TO TABLE ABBREVIATIONS:

1) *S.aureus* ATCC 25923 --*Staphylococus aureus* ATCC 25923

2) MRSA 15187 --Methicillin Resistant *Staphylococcus aureus*

3) *Ent. faecalis* ATCC 29212 --*Enterococcus faecalis* ATCC 29212

4) *Ent. faecium* 6A -- *Enterococcus faecium 6A Van®,Cipro®*

5) *Strep. pne.* ATCC 6303 --*Streptococcus pneumoniae* ATCC 6303

6) *Strep.pyog.* ATCC 19615 --*Streptococcus pyogenes*

7) S. epidermidis - *Staphylococcus epidermidis* ATCC 12228

Table-1

MIC OF THE SYNTHESIZED COMPOUNDS AGAINST 60 BACTERIAL CULTURES

S. No.	Organisms	MIC in (µg/ml)										
		Compound No. 1	Compound No. 2	Compound No. 3	Compound No. 15	Compound No. 12				Compound No. 23	Compound No. 21	Compound No. 22
1	*S. aureus* ATCC 25923	2	4	4	2	2				4	4	>16
2	*S. aureus* ATCC29213	2	4	1	8	2				4	4	>16
3	*S. aureus* SG 511	1	8	16	8	4				4	4	>16
4	*S. aureus* (MRSA) 15187	2	2	0.5	8	1				4	4	>16
5	*S. aureus* (MRSA) 21299	1	2	0.5	8	1				4	4	>16
6	*S. aureus* (MRSA) ST450	2	4	2	8	2				4	4	>16
7	*S. aureus* (MRSA 33) Cipro R	4	2	8	8	2				4	4	>16
8	*S. aureus* (MRSA) 562	2	4	8	8	4				4	4	>16
9	*S. aureus* (Smith 49951	2	4	2	8	4				4	4	>16
10	*S. epidermidis* ATCC 12228	<0.06	0.5	<0.015	1	<0.25				2	<0.125	1
11	*S.epidermidis* (MRSE) 23760	0.25	0.5	0.06	2	<0.25				2	0.25	4
12	*S.epidermidis* 823	<0.06	0.25	<0.015	2	<0.25				2	<0.125	4
13	*S.epidermidis* (MRSE)32965	<0.06	0.25	0.03	2	<0.25				4	0.25	4
14	*S.epidermidis* 358	<0.06	0.5	0.03	2	<0.25				2	<0.125	4
15	*S.haemo.*ATCC 29970	0.5	2	0.125	1	0.5				2	1	4
16	*S.warnerii* ST360	--	--	0.25	1	0.5				2	1	>16
17	*E.faecalis* 29212	2	8	4	4	1				4	1	>16
18	*E.faecalis* 21777	2	8	4	4	2				4	1	>16
19	*E.faecalis* 5B (VRE)	2	8	4	4	1				4	1	>16
20	*E.faecalis* SP 346 (VRE)	--	--	4	8	1				4	0.5	>16
21	*E.faecium* 6A (VRE)	2	8	8	8	2				4	4	>16
22	*E.faecium* 398(VRE)	2	8	4	8	2				4	4	>16
23	*E.faecium* 139	2	8	8	8	2				4	4	>16
24	*E.durans* 581	2	8	8	8	2				4	4	>16
25	*E.coli* 25922	>16	>16	>16	>16	>16				>16	>16	>16
26	*Salmonella* 205	>16	>16	>16	>16	>16				>16	>16	>16
27	*K. oxytoca* 49131	>16	>16	>16	>16	>16				>16	>16	>16
28	*P.aeruginosa* ATCC 27853	>16	>16	>16	>16	4				>16	>16	>16
29	*Serratia marcescens 12999*	>16	>16	>16	>16	>16				>16	>16	>16
30	*Acinetobacter 9956*	>16	>16	>16	>16	>16				>16	>16	>16

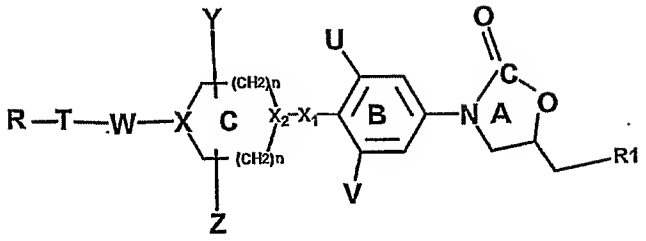
S. No.	Organisms	MIC in (µg/ml)									
		Compound No.1	Compound No. 2	Compound No.3	Compound No. 15	Compound No.12			Compound No. 23	Compound No. 21	Compound No 22
31	*S.pneumoniae AB-2*	2	8	8	16	1			1	2	4
32	*S.pneumoniae AB-3*	2	8	8	16	1			1	2	4
33	*S.pneumoniae AB4*	1	8	>16	16	1			2	4	16
34	*S.pneumoniae CSI221*	2	8	8	16	1			1	2	4
35	*S.pneumoniae AB 10*	2	8	>16	16	1			1	2	4
36	*S.pneumoniae AB 31*	4	8	8	16	2			2	2	4
37	*S.pneumoniae AB 14*	2	8	8	16	1			1	2	16
38	*S.pneumoniae 217*	4	4	>16	16	1			NG	NG	NG
39	*S.pneumoniae AB 16*	4	8	8	16	1			2	4	>16
40	*S.pneumoniae AB 17*	2	8	>16	16	1			2	4	>16
41	*S.pneumoniae AB 21*	2	8	>16	16	2			2	4	>16
42	*S.pneumoniae AB 22*	2	8	>16	16	2			2	4	>16
43	*S.pneumoniae AB 23*	2	8	>16	16	1			2	4	>16
44	*S.pneumoniae AB 24*	1	8	>16	16	1			2	4	>16
45	*S.pneumoniae AB 25*	1	8	>16	8	1			1	2	4
46	*S.pneumoniae* AB 29	2	8	--	8	2			NG	NG	NG
47	*S.pneumoniae* AB 30	2	4	8	16	2			1	1	8
48	*S.pneumoniae ATCC 49619*	2	8	8	16	2			1	2	4
49	*S.pneumoniae AB 34*	4	8	>16	16	4			2	4	16
50	*S.pneumoniae ATCC 6303*	2	8	8	16	1			2	4	>16
51	*S.pyogenes 19615*	0.25	4	8	16	1			2	0.5	8
52	*S.pyogenes 25147*	0.125	4	8	16	2			2	0.5	8
53	*S.pyogenes 20361*	--	--	8	16	1			2	4	8
54	*S.pneumoniae 1251*	2	4	>16	16	2			2	4	>16
55	*S pneumoniae 1294.*	--	--	---	NG	1			NG	NG	NG
56	*S.pneumoniae 1256*	0.25	4	4	16	1			2	8	>16
57	*S.pneumoniae 1275*	0.5	4	16	16	1			1	4	8
58	*Moraxella M1*	4	4	>16	>16	1			16	16	>16
59	*Moraxella cata. M2*	1	1	>16	>16	1			16	8	>16
60	*Moraxella M6*	2	4	>16	NG	1			8	>16	>16

The in vitro antibacterial activities of the compounds were demonstrated by the agar incorporation method (NCCLS M 7 and M 100-S8 documents). Briefly, the compounds were dissolved in DMSO and doubling dilution of the compounds were incorporated into Meer Hilton agar before solidification. Inoculum was prepared by suspending 4 to 5 colonies into 5 ml of normal saline solution and adjusting the turbility to 0.5 Macfarland turbidity standard tables (1.5×10^8 CFU/ml), after appropriate dilutions, 10^4 CFU/spot was transfered into the surface of dried plate and incubated for 18 hours (24 hours for MRSN studies). The concentration showing no growth of the inoculated culture was recorded as the MIC. Appropriate ATCC standard strains were simultaneously tested and result recorded only when the MIC's against standard antibiotics were within the acceptable range.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We Claim:

1. Compounds having the structure of Formula I:



FORMULA I

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, or metabolites, wherein

T is a five to seven membered heterocyclic ring, aryl, substituted aryl, bound to the ring **C** with a linker W, and the aryl and five membered heteroaryl rings are further substituted by a group represented by **R**, wherein R is selected from the group consisting of H, C_{1-6} alkyl, F, Cl, Br,I, -CN, COR_5,$COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, $CON (R_6, R_7)$, CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH = N-OR_{10}, -C=CH-R_5, OR_5, SR_5, $-C(R_9)=C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4, SR_4, wherein R_4 and R_5 are independently selected from H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl, heteroaryl; R_6 and R_7, are independently selected from H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently selected from H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl;

n is an integer in the range from 0 to 3;

X is H, CH, CH-S, CH-O, N, $CHNR_{11}$, wherein R_{11} is hydrogen, optionally substituted C_{1-2} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyl carboxy, aryl or heteroaryl;

X_1 is $(CH_2)_nS$, $(CH_2)_nO$, where n = 0 to 3; NR_{11} wherein R_{11} is the same as defined above, C=O, or C=S;

X_2 = CH or N;

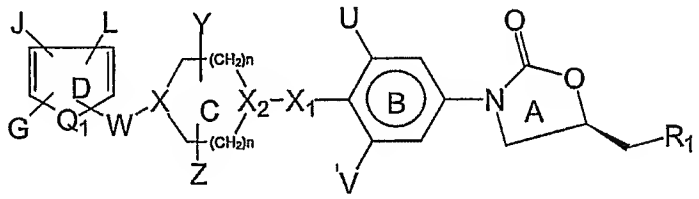
Y and Z are independently selected from hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl or C_{0-3} bridging group;

U and V are independently selected from hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

W is selected from CH_2, CO, CH_2NH, $-NHCH_2$, $-CH_2NHCH_2$, $-CH_2N(R_{11})CH_2-$, $CH_2(R_{11})N-$, $CH(R_{11})$, $CH_2(CO)$, NH, O, S, $N(R_{11})$, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, $N(R_{11})CSN(R_{11})$, SO_2, SO, wherein R_{11} is the same as defined above; and

R_1 is selected from the group consisting of $-NHC(=O)R_2$, $N(R_3, R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$, wherein R_2 is hydrogen, aryl, heteroaryl, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; or thioC_{1-6} alkyl; R_3, R_4 are independently selected from hydrogen, aryl, heteroaryl, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH.

2. Compounds having the structure of Formula II:



Formula II

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, or metabolites, wherein

R_1 is selected from the group consisting of $-NHC(=O)R_2$, $-N(R_3,R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$ wherein R_2, R_3, R_4 are independently hydrogen, aryl, heteroaryl, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I, OH;

U and **V** are independently selected from hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

Y and Z are independently selected from hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{0-3} bridging group;

X is selected from H, CH, CH-S, CH-O or N;

X_1 is $(CH_2)_nS$, $(CH_2)_nO$, where n = 0 to 3; NR_{11}, wherein R_{11} is hydrogen, optionally substituted C_{1-2} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyl carboxy, aryl or heteroaryl, C=O, or C=S;

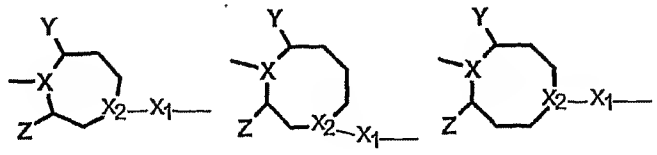
X_2 = CH or N;

W is independently selected from CH_2, C=O, CH_2NH, $NHCH_2$, CH_2NHCH_2, $CH_2N(R_{11})CH_2$, $CH_2N(R_{11})$, $CH(R_{11})$, $CH_2(C=O)$, NH, O, S, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, SO_2, SO, $N(R_{11})$, $N(R_{11})C(=S)N(R_{11})$, wherein R_{11} is the same as defined above;

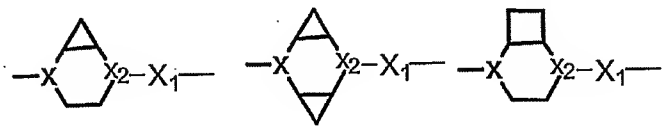
Q_1 is selected from O, S or NR_{11}, wherein R_{11} is as defined earlier;

G, J, L are independently selected from H, C_{1-6} alkyl, F, Cl, Br,I, –CN, COR_5,$COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, CON (R_6, R_7), CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH = N-OR_{10}, -C=CH-R_5, OR_5, SR_5, $-C(R_9)=C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4, SR4, wherein R_4, R_5 are independently selected from H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl, heteroaryl; R_6 and R_7, are independently selected from H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently selected from H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl, heteroaryl; except when W=CO, Q_1=O, S, X=N, X_2=CH, X_1=O, and G, J, L=H.

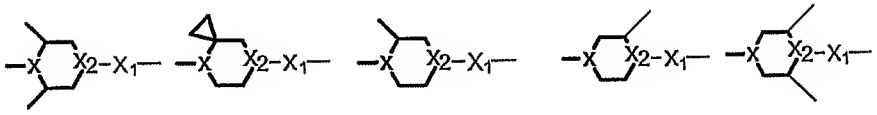
3. The compound according to claim 2 wherein in Formula II, ring C is 6-8 membered in size and the ring may have either two or three carbon atoms between each nitrogen atom comprising of:



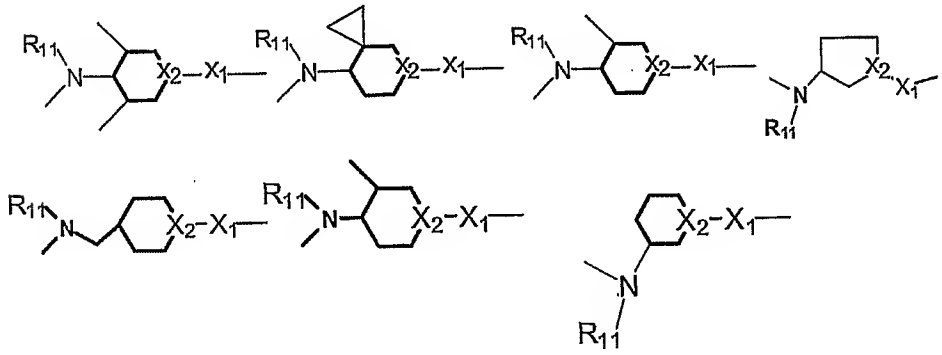
and the ring C may be bridged to form a bicyclic system as shown below,



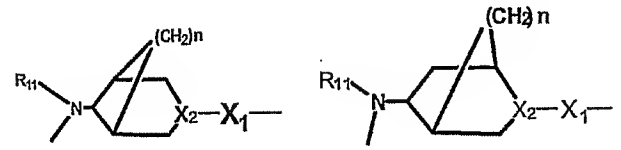
4. The compound according to claim 2 wherein in Formula II, ring C is substituted at positions Y and Z with alkyl groups, cycloalkyl groups, fluoro group, carboxylic and corresponding esters, amides, substituted alkyls or bridging alkyl group as shown below,

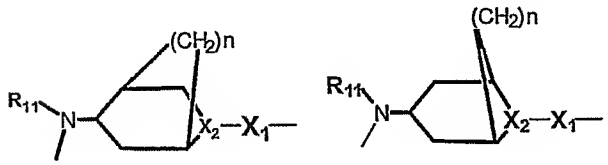


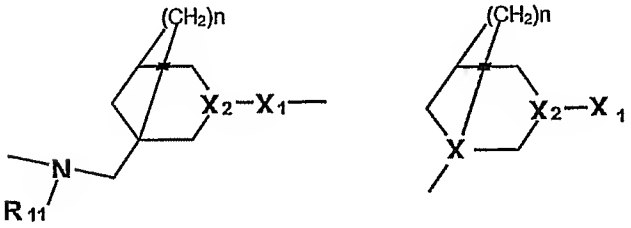
5. The compound according to claim 2 wherein in Formula II, ring C is 6 membered in size and X is -CH-(NHR), or >CCH_2NHR-, the ring C is selected from the group consisting of the following rings wherein R_{11} is the same as defined earlier,



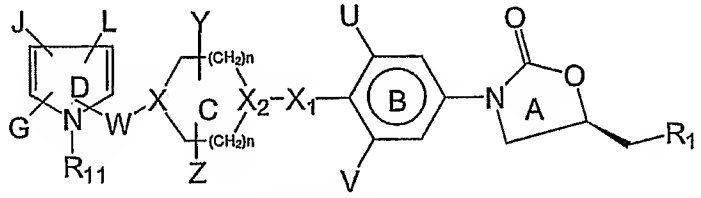
or in addition to the above, the ring C includes the following structures:







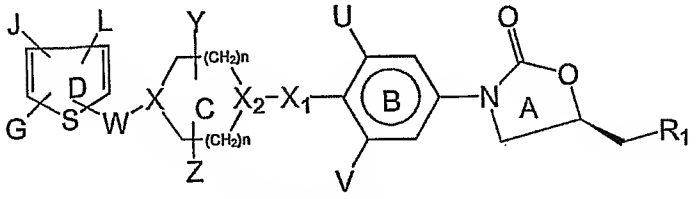
6. The compound according to claim 2 having the structure of Formula III,



FORMULA III

wherein U, V, Y, Z, X, X_1, X_2, R_1, R_{11}, W, G, J, L and n are as defined earlier.

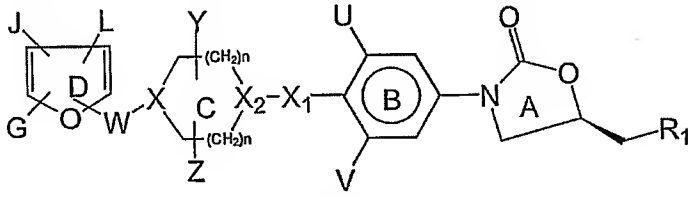
7. The compound according to claim 2 having the structure of Formula IV,



FORMULA IV

wherein U, V, Y, Z, X, X_1, X_2, R_1, W, G, J, L and n are as defined earlier.

8. The compound according to claim 2 having the structure of Formula V,



FORMULA V

wherein U, V, Y, Z, X, X_1, X_2, R_1, W, G, J, L and n are as defined earlier.

9. A compound selected from the group consisting of :

(S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl-(5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.1)

(S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.2)

(S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl-(4-bromo-5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.3)

(S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(4-bromo-5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.4)

(S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(4-morpholino-5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.5)

(S)-N-[[3-[3-Fluoro-4-[N-1-[2-thienyl-{4-(N-4-methylpiperazin-1-yl)-5-nitro} methyl]piperidinyl -4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.6)

(S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(4-dimethylamino-5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.7)

(S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl-(4-isopropyl-5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.8)

(S)-N-[[3-[3-Fluoro-4-[N-1-[2-furyl-{5-(2-nitro)phenyl} methyl]piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.9)

(S)-N-[[3-[3-Fluoro-4-[N-1-[2-furyl-{5-(3-nitro)phenyl} methyl]piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.10)

(S)-N-[[3-[3-Fluoro-4-[N-1-{3-thienyl-(2-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.11)

(S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl-(5-nitro) methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]thioacetamide (Compound No.12)

(S)-N-[[3-[3-Fluoro-4-[N-1-{(benzo(b)furan-2-yl)methyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.13)

(S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(5-nitro)}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.14)

(S)-N-[[3-[3-Fluoro-4-[N-1-[1-{2-furyl-(5-nitro)-}-ethyl] piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.15)

(S)-N-[[3-[3-Fluoro-4-[N-1-{2-furyl-(5-nitro)carbonyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.16)

(S)-N-[[3-[3-Fluoro-4-[N-1-{(benzo(b)furan-2-yl)carbonyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.17)

(S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(5-nitro)carbonyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.18)

(S)-N-[[3-[3-Fluoro-4-[N-1-{2-thienyl-(5-nitro)thiocarbonyl}piperidinyl-4-oxy]phenyl]-2-oxo-5-oxozolidinyl]methyl]thioacetamide (Compound No.19)

(S)-N-[[3-[3-Fluoro-4-[{(1α,5α,6α)-3-t-butoxycarbonyl-3-azabicyclo[3.1.0]hexan-6-yl}-methyloxyl]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.20)

(S)-N-[[3-[3-Fluoro-4-[[(1α,5α,6α)-3-{2-furyl(5-nitro)methyl}-3-azabicyclo[3.1.0]hexan-6-yl]-methyloxyl]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.21)

(S)-N-[[3-[3-Fluoro-4-[[(1α,5α,6α)-3-{2-thienyl(5-nitro)methyl}-3-azabicyclo[3.1.0]hexan-6-yl]-methyloxyl]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.22)

(S)-N-[[3-[3-Fluoro-4-[{(1α,5α,6α)-3-(5-nitro-2-thienyl)-3-azabicyclo[3.1.0]hexan-6-yl}-methyloxyl]phenyl]-2-oxo-5-oxozolidinyl]methyl]acetamide (Compound No.23)

(S)-N-[[3-[3-Fluoro-4-[N-1-(4-t-butoxycarbonyl)piperazinylcarbonyl] phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (Compound No.24)

(S)-N-[[3-[3-Fluoro-4-[N-1-[4-{2-furyl-(5-nitro)methyl}]piperazinylcarbonyl] phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (Compound No.25)

(S)-N-[[3-[3-Fluoro-4-[N-1-[4-{2-thienyl-(5-nitro)methyl}]piperazinylcarbonyl] phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (Compound No.26)

(S)-N-[[3-[3-Fluoro-4-[N-1-[4-{2-thienyl-(5-nitro)}]piperazinylcarbonyl] phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (Compound No.27).

10. A pharmaceutical composition comprising the compound of claims 1, 2 or 9 and a pharmaceutical acceptable carrier.

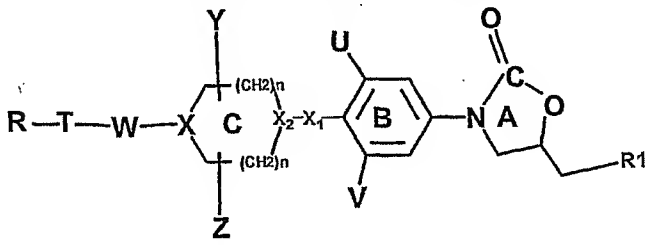
11. A pharmaceutical composition comprising a pharmaceutically effective amount of compound according to claims 1, 2 or 9 or a physiologically acceptable acid addition salt thereof with a pharmaceutically acceptable carrier for treating microbial infections.

12. A method of treating or preventing microbial infections in a mammal comprising administering to said mammal, the pharmaceutical composition according to claim 11.

13. The method according to claim 12 wherein the microbial infections are caused by gram-positive and gram-negative bacteria.

14. The method according to claim 13 wherein the gram-positive bacteria are selected from the group consisting of staphylococcus spp., streptococcus spp., listeria spp. and legionella spp.

15. A method of treating or preventing aerobic and anaerobic bacterial infections in a mammal comprising administering to said mammal, a therapeutically effective amount of a compound having the structure of Formula I



FORMULA I

or its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein

T is a five to seven membered heterocyclic ring, aryl, substituted aryl, bound to the ring **C** with a linker W, and the aryl and five membered heteroaryl rings are further substituted by a group represented by **R**, wherein R is selected from the group consisting of H, C_{1-6} alkyl, F, Cl, Br,I, –CN, COR_5,$COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, CON (R_6, R_7), CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH = N-OR_{10}, -C=CH-R_5, OR_5, SR_5, -$C(R_9)$=$C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4, SR_4, wherein R_4 and R_5 are independently selected from H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl, heteroaryl; R_6 and R_7, are independently selected from H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently selected from H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl;

n is an integer in the range from 0 to 3;

X is H, CH, CH-S, CH-O, N, $CHNR_{11}$, wherein R_{11} is hydrogen, optionally substituted C_{1-2} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyl carboxy, aryl or heteroaryl;

X_1 is $(CH_2)_nS$, $(CH_2)_nO$, where n = 0 to 3; NR_{11} wherein R_{11} is the same as defined above, C=O, or C=S;

X_2 = CH or N;

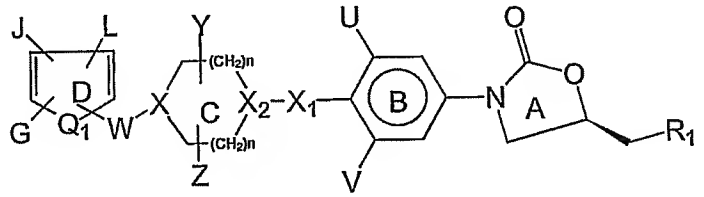
Y and Z are independently selected from hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl or C_{0-3} bridging group;

U and V are independently selected from hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

W is selected from CH_2, CO, CH_2NH, $-NHCH_2$, $-CH_2NHCH_2$, $-CH_2N(R_{11})CH_2-$, $CH_2(R_{11})N-$, $CH(R_{11})$, $CH_2(CO)$, NH, O, S, $N(R_{11})$, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, $N(R_{11})CSN(R_{11})$, SO_2, SO, wherein R_{11} is the same as defined above; and

R_1 is selected from the group consisting of $-NHC(=O)R_2$, $N(R_3, R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$, wherein R_2 is hydrogen, aryl, heteroaryl, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; or thioC_{1-6} alkyl; R_3, R_4 are independently selected from hydrogen, aryl, heteroaryl, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH.

16. A method of treating or preventing aerobic and anaerobic bacterial infections in a mammal comprising administering to said mammal, a therapeutically effective amount of a compound having the structure of Formula II



FORMULA II

or its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, or metabolites, wherein

R_1 is selected from the group consisting of $-NHC(=O)R_2$, $-N(R_3,R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$ wherein R_2, R_3, R_4 are independently hydrogen, aryl, heteroaryl, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I, OH;

U and **V** are independently selected from hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

Y and **Z** are independently selected from hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{0-3} bridging group;

X is selected from H, CH, CH-S, CH-O or N;

X_1 is $(CH_2)_nS$, $(CH_2)_nO$, where n = 0 to 3; NR_{11}, wherein R_{11} is hydrogen, optionally substituted C_{1-2} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyl carboxy, aryl or heteroaryl, C=O, or C=S;

X_2 = CH or N;

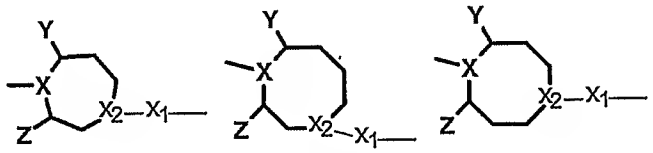
W is independently selected from CH_2, C=O, CH_2NH, $NHCH_2$, CH_2NHCH_2, $CH_2N(R_{11})CH_2$, $CH_2N(R_{11})$, $CH(R_{11})$, $CH_2(C=O)$, NH, O, S, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, SO_2, SO, $N(R_{11})$, $N(R_{11})C(=S)N(R_{11})$, wherein R_{11} is the same as defined above;

Q_1 is selected from O, S or NR_{11}, wherein R_{11} is as defined earlier;

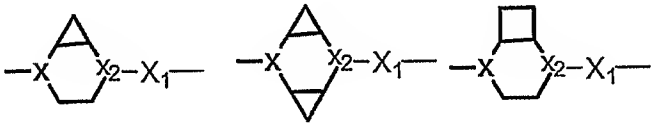
G, J, L are independently selected from H, C_{1-6} alkyl, F, Cl, Br,I, –CN, COR_5,$COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, CON (R_6, R_7), CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH = N-OR_{10}, -C=CH-R_5, OR_5, SR_5, $-C(R_9)=C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4, SR_4; wherein R_4, R_5 are independently selected from H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl, heteroaryl; R_6 and R_7, are independently selected from H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently selected from H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}=

H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl, heteroaryl; except when W=CO, Q_1=O, S, X=N, X_2=CH, X_1=O, and G, J, L=H.

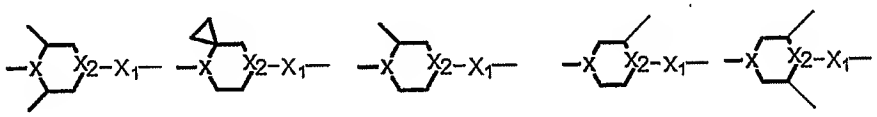
17. The method according to claim 16 wherein in Formula II, ring C is 6-8 membered in size and the ring may have either two or three carbon atoms between each nitrogen atom comprising of:



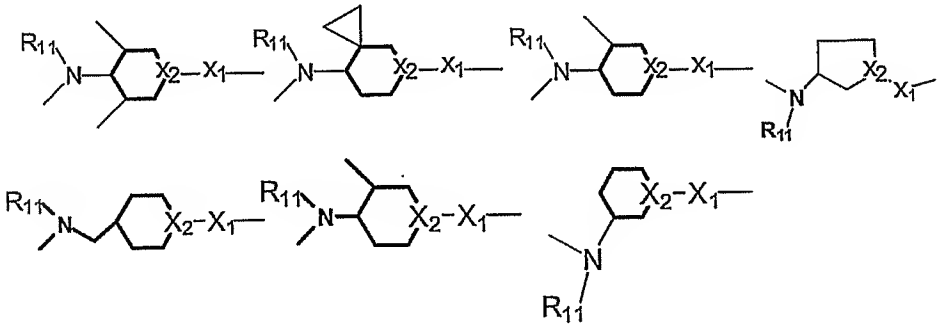
and ring C may be bridged to form a bicyclic system as shown below,



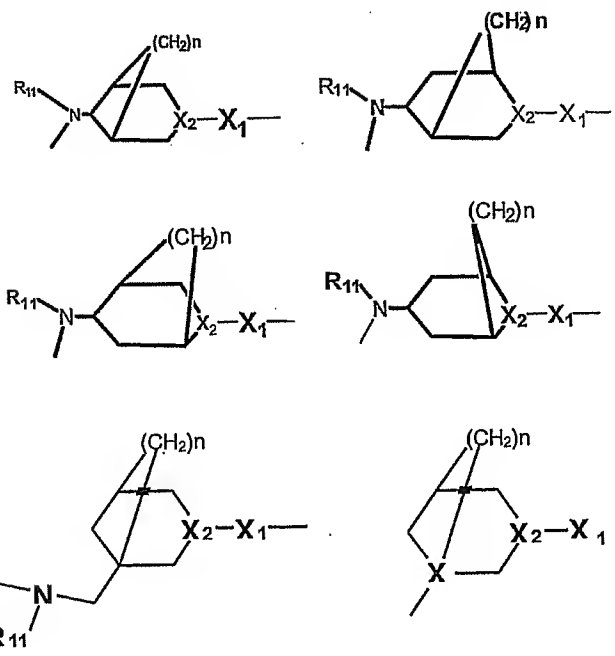
18. The method according to claim 16 wherein in Formula II, ring C is substituted at positions Y and Z with alkyl groups, cycloalkyl groups, fluoro group, carboxylic and corresponding esters, amides, substituted alkyls or bridging alkyl groups as shown below,



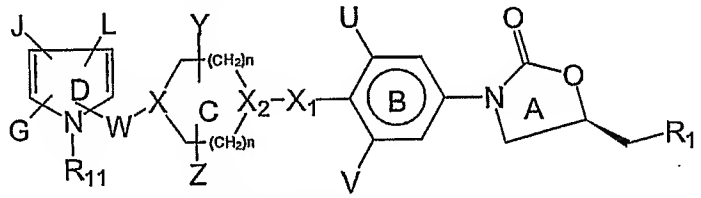
19. The method according to claim 16 wherein in Formula II, ring C is 6 membered in size and X is -CH-(NHR), or >CCH_2NHR-, the ring C is selected from the group consisting of the following rings wherein R_{11} is the same as defined earlier,



or in addition to the above, the ring C includes the following structures:



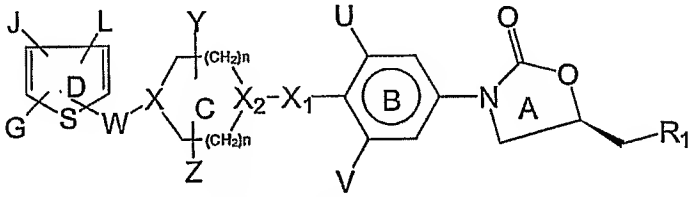
20. The method according to claim 16 having the structure of Formula III,



FORMULA III

wherein U, V, Y, Z, X, X1, X_2, R_1, R_{11}, W, G, J, L and n are as defined earlier.

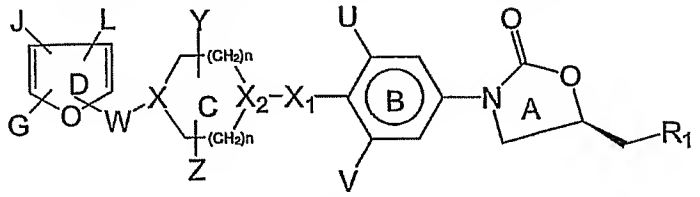
21. The method according to claim 16 having the structure of Formula IV,



FORMULA IV

wherein U, V, Y, Z, X, X_1, X_2, R_1, W, G, J, L and n are as defined earlier.

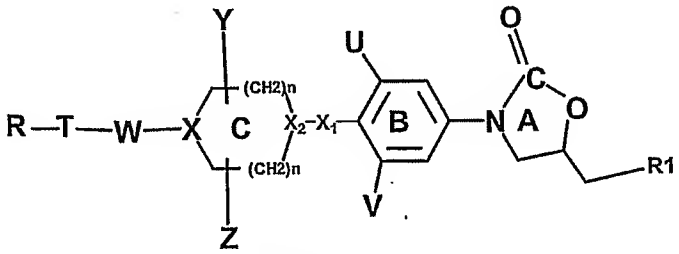
22. The compound according to claim 16 having the structure of Formula V,



FORMULA V

wherein U, V, Y, Z, X, X_1, X_2, R_1, W, G, J, L and n are as defined earlier.

23. A process for preparing a compound of Formula I,



FORMULA I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, or metabolites, wherein

T is a five to seven membered heterocyclic ring, aryl, substituted aryl, bound to the ring **C** with a linker W, and the aryl and five membered heteroaryl rings are further substituted by a group represented by **R**, wherein R is selected from the group consisting of H, C_{1-6} alkyl, F, Cl, Br,I, –CN, COR_5,$COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, $CON(R_6, R_7)$, CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH = N-OR_{10}, -C=CH-R_5, OR_5, SR_5, $-C(R_9)=C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4, SR_4, wherein R_4 and R_5 are independently selected from H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl, heteroaryl; R_6 and R_7, are independently selected from H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently selected from H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl or heteroaryl;

n is an integer in the range from 0 to 3;

X is H, CH, CH-S, CH-O, N, $CHNR_{11}$, wherein R_{11} is hydrogen, optionally substituted C_{1-2} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyl carboxy, aryl or heteroaryl;

$\mathbf{X_1}$ is $(CH_2)_nS$, $(CH_2)_nO$, where n = 0 to 3; NR_{11} wherein R_{11} is the same as defined above, C=O, or C=S;

$\mathbf{X_2}$ = CH or N;

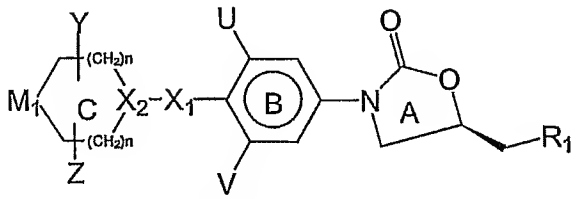
Y and Z are independently selected from hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl or C_{0-3} bridging group;

U and V are independently selected from hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

W is selected from CH_2, CO, CH_2NH, $-NHCH_2$, $-CH_2NHCH_2$, $-CH_2N(R_{11})CH_2-$, $CH_2(R_{11})N-$, $CH(R_{11})$, $CH_2(CO)$, NH, O, S, $N(R_{11})$, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, $N(R_{11})CSN(R_{11})$, SO_2, SO, wherein R_{11} is the same as defined above; and

$\mathbf{R_1}$ is selected from the group consisting of $-NHC(=O)R_2$, $N(R_3, R_4)$, $-NR_2C(=S)R_3$, $-NR_2C(=S)SR_3$, wherein R_2 is hydrogen, aryl, heteroaryl, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH; or thioC_{1-6} alkyl; R_3, R_4 are independently selected from hydrogen, aryl, heteroaryl, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH,

which comprises reacting an amine of Formula VI



Formula VI

with a heteroatomic group of Formula R-T-W-R_{12} wherein T, W, R_1, U, V, Y, Z, X_2, X_1, and n are the same as defined earlier and M_1 is selected from the group consisting of NH, NHR_{14}, CH_2NHR_{14}, $CH\text{-}CH_2NHR_{14}$, $-CCH_2\text{-}NHR_{14}$ wherein R_{14} is H, ethyl, methyl, isopropyl, acetyl, cyclopropyl, or alkoxy and R_{12} is a suitable

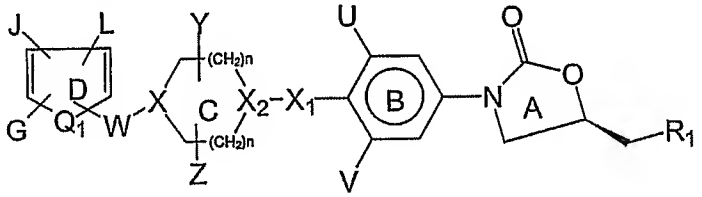
leaving group selected from the group consisting of fluoro, chloro, bromo, iodo, SCH_3, $-SO_2CH_3$, $-SO_2CF_3$, Tos and OC_6H_5.

24. The process of claim 23 wherein the amine of Formula VI reacts with a heteroaromatic compound of Formula R-T-W-R_{12} in the presence of a base selected from the group consisting of potassium carbonate, N-ethyldiisopropylamine and dipotassium hydrogen phosphate.

25. The process of preparing a compound of Formula I of claim 23, wherein W=CH_2 and R-T-W-R_{12} is a five membered heterocyclic ring with aldehyde group and the compound of Formula I is produced by reductive amination.

26. The process for preparing a compound of Formula I of claim 23 wherein W=CO and R-T-W-R_{12} is a five membered heterocyclic ring with carboxylic acid and amino compound of Formula VI is acylated with activated esters in the presence of condensing agents consisting of 1,3-dicyclohexyl carbodiimide (DCC) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDC).

27. A process for preparing a compound having the structure of Formula II:



FORMULA II

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, polymorphs, enantiomers, diastereomers, N-oxides, prodrugs or metabolites, wherein

R_1 is selected from the group consisting of $-NHC(=O)R_2$; $-N(R_3,R_4)$; $-NR_2C(=S)R_3$; $-NR_2C(=S)SR_3$ wherein R_2, R_3, R_4 are independently hydrogen, aryl, heteroaryl, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted one or more of F, Cl, Br, I, OH,

U and **V** are independently selected from hydrogen, optionally substituted C_{1-6} alkyl, F, Cl, Br, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I;

Y and **Z** are independently selected from hydrogen, C_{1-6} alkyl, C_{3-12} cycloalkyl, C_{0-3} bridging group;

X is selected from H, CH, CH-S, CH-O or N;

X_1 is $(CH_2)_nS$, $(CH_2)_nO$, where n = 0 to 3; NR_{11}, wherein R_{11} is hydrogen, optionally substituted C_{1-2} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyl carboxy, aryl or heteroaryl, C=O, or C=S;

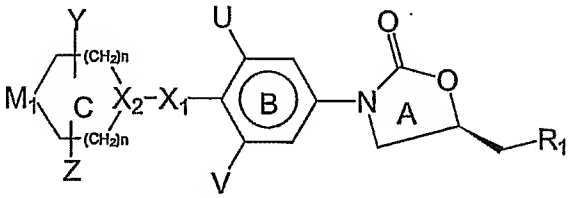
X_2 = CH or N;

W is independently selected from CH_2, C=O, CH_2NH, $NHCH_2$, CH_2NHCH_2, $CH_2N(R_{11})CH_2$, $CH_2N(R_{11})$, $CH(R_{11})$, $CH_2(C=O)$, NH, O, S, $(CO)CH_2$, $N(R_{11})CON(R_{11})$, SO_2, SO, $N(R_{11})$, $N(R_{11})C(=S)N(R_{11})$, wherein R_{11} is the same as defined above;

Q_1 is selected from O, S or NR_{11}, wherein R_{11} is as defined above;

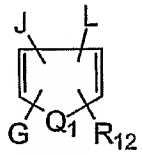
G, J, L are independently selected from H, C_{1-6} alkyl, F, Cl, Br,I, –CN, COR_5,$COOR_5$, $N(R_6,R_7)$, $NHCOC(R_8, R_9, R_{10})$, CON (R_6, R_7), CH_2NO_2, NO_2, CH_2R_8, CHR_9, -CH = N-OR_{10}, -C=CH-R_5, OR_5, SR_5, $-C(R_9)=C(R_9)NO_2$, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_4, SR_4, wherein R_4, R_5 are independently selected from H, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted with one or more of F, Cl, Br, I or OH, aryl, heteroaryl; R_6 and R_7, are independently selected from H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy; R_8 and R_9 are independently selected from H, C_{1-6} alkyl, F, Cl, Br, I, C_{1-12} alkyl substituted with one or more of F, Cl, Br, I, OR_5, SR_4, $N(R_6,R_7)$; R_{10}= H, optionally substituted C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkyl, aryl, heteroaryl; except when W=CO, Q_1=O, S, X=N, X_2=CH, X_1=O and G, J, L=H,

comprising reacting a compound Formula VI



Formula VI

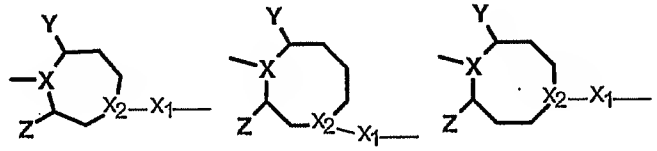
with a heteroaromatic compound of Formula VII



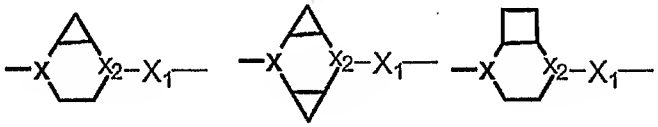
Formula VII

wherein R_1, U, V, X_1, X_2, M_1, Y, Z, n, R_{12}, Q_1, G, J and L are as defined earlier.

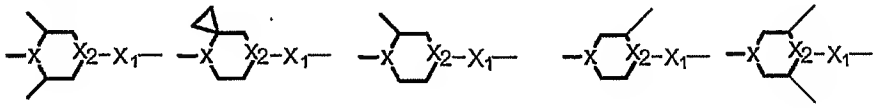
28. The process according to claim 27 wherein in Formula II, ring C is 6-8 membered in size and the ring may have either two or three carbon atoms between each nitrogen atom comprising of:



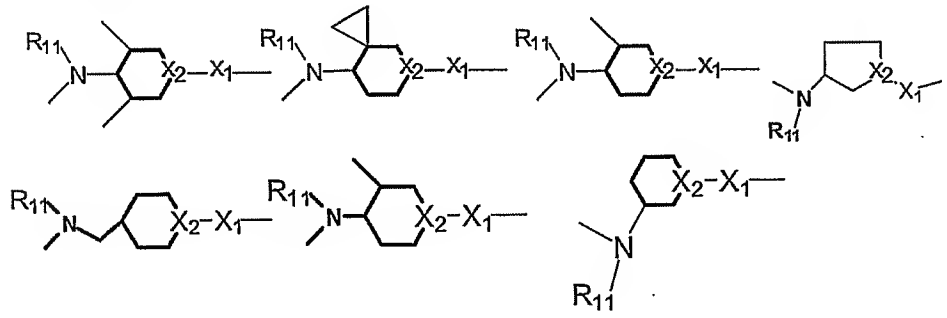
and ring C may be bridged to form a bicyclic system as shown below,



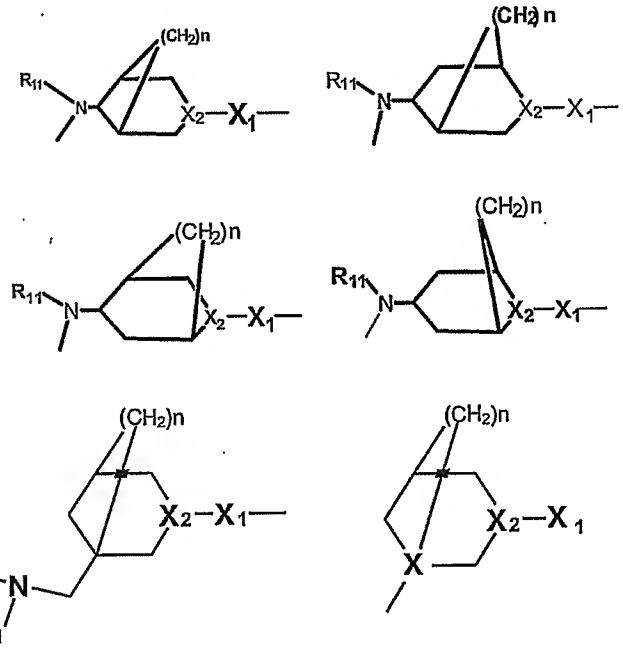
29. The process according to claim 27 wherein in Formula II, ring C is substituted at positions Y and Z with alkyl groups, cycloalkyl groups, fluoro group, carboxylic and corresponding esters, amides, substituted alkyls or bridging alkyl groups as shown below,



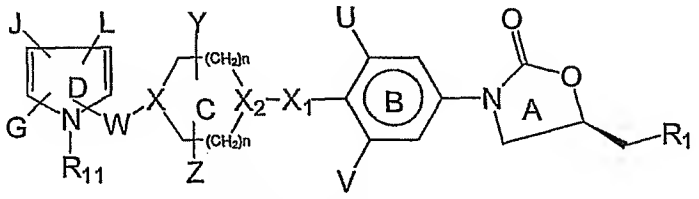
30. The process according to claim 27 wherein in Formula II, ring C is 6 membered in size and X is -CH-(NHR), or >CCH_2NHR-, ring C is slected from the group consisting of the following rings wherein R_{11} is the same as defined earlier,



or in addition to the above, the ring C includes the following structures:



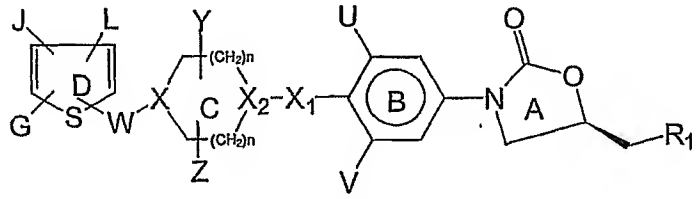
31. The process according to claim 27 having the structure of Formula III,



FORMULA III

wherein U, V, Y, Z, X, X_1, X_2, R_1, R_{11}, W, G, J, L, and n are as defined earlier.

32. The process according to claim 27 having the structure of Formula IV,

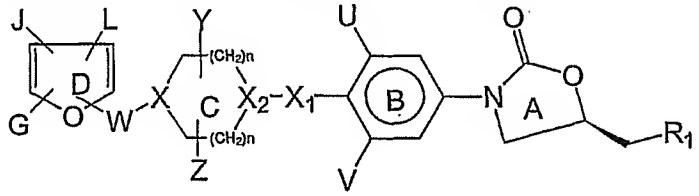


FORMULA IV

wherein U, V, Y, Z, X, X_1, X_2, R_1, W, G, J, L, and n are as defined earlier.

33. The process

34. according to claim 27 having the structure of Formula V,



FORMULA V

wherein U, V, Y, Z, X, X_1, X_2, R_1, W, G, J, L, and n are as defined earlier.

34. The process of claim 27 wherein the reaction is carried out in a suitable solvent selected from the group consisting of dimethylformamide, dimethylacetamide, ethanol, dimethylsulfoxide, acetonitrile or ethyleneglycol at a suitable temperature in the range of about –70°C to about 180°C in the presence of a suitable base selected from the group consisting of triethylamine, N-ethyl diisopropylamine, potassium carbonate, sodium carbonate and dipotassium hydrogen phosphate.

35. The process of claim 27 wherein Formula VII is 5-nitro-2-furaldehyde and the reductive alkylation of the amine of Formula VI is performed with a reducing agent.

36. The process of claim 27 wherein Formula VII is 5-nitro-2-furoic acid.

INTERNATIONAL SEARCH REPORT

Inte ɪnat Application No
PCT/IB 03/00429

A. CLASSIFICATIDN OF SUBJECT MATTER
IPC 7 C07D263/20 C07D413/12 C07D413/14 A61K31/422 A61K31/454 A61K31/497 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation seerched other than minimum documentation to the extent that such documents are included in the fields seerched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DDCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	WO 01 46164 A (ORTHO-MCNEIL PHARMACEUTICAL, INC.) 28 June 2001 (2001-06-28) cited in the application the whole document ---	1-36
X,Y	WEIDNER-WELLS M A ET AL: "Novel piperidinyloxy oxazolidinone antimicrobial agents" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 11, no. 14, 23 July 2001 (2001-07-23), pages 1829-1832, XP002256720 cited in the application the whole document ---	1-36

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[X] Further documents are listed in the continuetion of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document detining the general state of the art which is not considered to be of particuler relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication dete of another citetion or other speciel reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in contlict with the application but cited to understand the principle or theory underlying the invention

"X" document of particuler relevance; the cleimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the cleimed invention cannot be considered to involve en inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the eame patent family

Date of the actual completion of the International search	Date of mailing of the international search report
6 October 2003	17/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X,Y	WEIDNER-WELLS M A ET AL: "Novel piperidinyloxy oxazolidinone antibacterial agents. Diversification of the N-substituent" BIOORGANIC & MEDICINAL CHEMISTRY, vol. 10, no. 7, July 2002 (2002-07), pages 2345-2351, XP002256721 the whole document	1-36
Y	WO 03 007870 A (RANBAXY LABORATORIES LIMITED) 30 January 2003 (2003-01-30) the whole document	1-36
Y	US 2002/103186 A1 (MEHTA A ET AL) 1 August 2002 (2002-08-01) the whole document	1-36

INTERNATIONAL SEARCH REPORT

national application No.
PCT/IB 03/00429

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1, 2, 15-21, 23, 24, 27-36 (all in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 2, 15-21, 23, 24, 27-36 (all in part)

The scope of claims 1, 2, 15-21, 23, 24 and 27-36, in as far as the expressions "prodrugs" and "metabolites" are explicitly or implicitly concerned, is so unclear (Artice 6 PCT) that a meaningful international search is impossible with regard to these expressions.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ɔnal Application No
PCT/IB 03/00429

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0146164 A	28-06-2001	AU 2261701 A	03-07-2001
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		EP 1246810 A1	09-10-2002
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		CZ 20030228 A3	18-06-2003
		EP 1303511 A1	23-04-2003
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